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Genetic mutations associated with hereditary breast cancer in Nicaraguan women

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ABSTRACT

Introduction: The etiology of breast cancer is multifactorial, however, it has been evidenced that most are sporadic and 5 to 10% of genetic origin. The genes known to date and associated with a hereditary predisposition to breast cancer have been classified according to their function in genes of high, moderate, and low penetrance.

Objective: To determine genetic mutations associated with hereditary breast cancer in Nicaraguan women.

Materials and Method: 39 women with histopathological diagnosis of breast cancer were recruited to participate in the study, with prior informed consent. Five ml of peripheral blood was taken from each of the patients for DNA extraction, then genetic testing of the BRCA1, BRCA2, Tp53, PALB2, CDH1, PTEN, and CHEK2 genes was performed, determining their clinical significance by comparing the sequences with the Breast Cancer Information Core (BIC) and ClinVar databases.

Results: 10.2% (4/39) of the patients studied carried a pathogenic mutation in BRCA2 (5%), Tp53, and PALB2 (2.5% respectively), associated with hereditary breast cancer. Variations of benign clinical significance, uncertain, variants that have not yet been reported in the databases, and others with pathogenicity conflict were also identified.

Conclusion: It is necessary and important to include molecular diagnosis in Nicaraguan patients at risk of developing breast cancer of hereditary origin, for their well-being and that of their families, achieving an early diagnosis, improving therapy, and follow-up. Therefore, we recommend the integration of genetic screening for Nicaraguan women at risk of developing this disease and for those who already have it.

INTRODUCTION

The etiology of breast cancer is multifactorial, however, it has been evidenced that most of them are sporadic and 5-10% of genetic origin. (Apostolou, P., & Fostira, F. 2013; Narod, S., & Rodriguez, A, 2011) The genes known to date and associated with a hereditary predisposition to breast cancer have been classified according to their function into; high penetrance genes (BRCA1/2, Tp53, PTEN, STK11, CDH1), which encode tumor suppressor proteins responsible for maintaining the genomic stability of the cell, moderate penetrance genes (ATM, CHEK2, PALB2, BARD1, BRIP1, MRE11A) encoding proteins involved in repairing damaged DNA by

homologous recombination with other proteins and low penetrance genes (FGFR2, LSP1, MAP3K1, TGFB1, TOX3, VEGF, PGR, KRAS, and PARP) that are being studied. (Larsen et al., 2014; Walsh et al., 2016; Tung et al., 2016).

The most studied genes for their function are BRCA1 and BRCA2, as they perform vital cellular functions in DNA homologous repair. (Mahdavi et al., 2019) Women carrying mutations in these genes have an increased risk of developing breast cancer at an early and contralateral age compared to the risk in the general population. (Fernandez, A & Reigosa, A. 2016)

Vaca-Paniagua et al., (2012) indicate that despite the outstanding relevance of genetic screening for pathogenic variants in patients with a history of hereditary breast cancer, this practice is not common in Latin American public institutions. Zabala et al., (2019) also suggest that this is due to limited resources in developing countries.

Evaluation of genetic variations in Latin America

Breast cancer mortality in Latin American countries is higher than in industrialized countries (14% vs. 7%, respectively) and a prevalence that varies between 8% and 14%, with stages II and III being the most frequent, high histological grade, triple-negative and HER2 BC (Villarreal-Garza et al., 2013) considering that it is probably related to the different screening strategies, access to treatment and management of the disease. (Chavarri-Guerra, Villareal-Garza et al., 2012; Tung et al., 2016).

The most recent genetic studies on hereditary breast cancer in Latin America have been published in Brazil (da Costa et al., 2020), Mexico (Zayas-Villanueva et al., 2019); Chile (Adaniel et al., 2019), Argentina (Cerratini et al., (2019), Colombia (Cock-Rada et al., 2018), Peru (Buleje et al., (2017) and Uruguay (Della et al., (2017). In Central America, only Costa Rica has published two studies. (Gutierrez, 2012; Garcia et al., 2012) In the Caribbean, there has been important research on hereditary breast cancer that has contributed to the early diagnosis of women at risk (George et al., 2021), in the Bahamas (Bagherzadeh et al., 2020), in Jamaica (Lerner-Ellis et al., 2017), Trinidad and Tobago (Donenberg et al., 2016).

These studies have managed to identify founder mutations in different countries such as Brazil (BRCA1 5382insC and BRCA2 c.156_157insAlu), Colombia (BRCA1 3450del4, A1708E, and BRCA2 3034del4), Chile (185delAG), Mexico (BRCA1 from exon9-12), Bahamas (943ins10). Likewise, there are reports in Latin women residing in Southern California (BRCA1 185delAG, from exon9-12, IVS5+1G>AS, 955x and R1443x) (Ashton-Prolla, P., & Vargas, F. R. (2014); Weitzel et al., 2013; Alvarez et al., 2017) allowed using a multipanel (HISPANEL) in Latin women with apparent risk to hereditary breast cancer (Chavarri-Guerra, Villareal-Garza, et al., 2012; Quezada et al., 2018; Villarreal-Garza, Alvarez-Gomez, et al., 2015, Alvarez et al., 2017).

The 185delAG (BRCA1) mutation has been reported in Peru (Abugattas et al., 2015) Mexico, Chile, and the Bahamas as recurrent, this being the most frequent founder mutation in the Jewish population. (Villarreal-Garza, Weitzel et al., 2015)

Jara et al., (2017) reported the 3036delACAA variant in BRCA2 as one of the six most frequent mutations among Latin American women. This variant has been reported as recurrent in studies conducted in Argentina (Solano et al., 2012), Colombia (Hernández et al., 2014; Torres et al., 2017); Venezuela (Lara et al., 2012); and Mexico (Torres-Meiía et al., 2015), it is also one of the ten most frequent mutations in all races or ethnicities. (Rebbeck et al., 2018).

Worldwide, there are important advances in the analysis of high-risk non-BRCA genes, moderate and low penetrance genes to achieve improved individual risk prediction of family history of breast cancer. Wendt, C., & Margolin, S. (2019).

TP53: Inherited mutations in this gene are associated with LFS (Apostolou, P., & Fostira, F. 2013). According to Walsh et al. (2016), indicates that the determination of mutations in this gene is justifiable in the presence of family history of breast cancer and BRCA negative.

PALB2: it is another gene incorporated in the multiethnic analysis to determine mutations associated with breast cancer due to its vital function, as it helps control the rate of cell growth and division by interacting with the BRCA2 protein working together to correct and repair damaged DNA breaks. (Apostolou, P., & Fostira, F. 2013)

Cock-Rada et al. (2018) studied the frequency and type of mutations in multiple genes associated with hereditary breast cancer, finding that 22.4% of cases carried a deleterious germline mutation in a cancer susceptibility gene: BRCA1 (7), BRCA2 (8), PALB2 (1), ATM (1), MSH2 (1), and PMS2 (1). One BRCA2 mutation (c.9246dupG) was recurrent in five unrelated individuals and had not been previously reported in the country. They observed a very low frequency of the Colombian founder BRCA1/ 2 mutation (1.2%) but found mutations in other genes such as PALB2, ATM, MSH2, and PMS2. They conclude that their results highlight the importance of performing multiple gene panel testing, including full BRCA1/ 2 analysis in patients with high-risk breast and/or ovarian cancer in Colombia.

Adaniel et al. (2019) studied genetic variants in Chilean women found that 8.6% presented pathogenic variants in non-BRCA genes: three pathogenic variants in CHEK2 (c.1100 delC, c.1344delT, c.1344delT), one variant in CDH1 (c.1565+2dupT), four variants in PALB2 (c.860dupT, c.3256C>T, c.2964delA, c.2218C>T) and one variant in RAD51D (c.216C>A).

Gallardo-Alvarado et al. (2019) studied the prevalence of mutations in the TP53 gene in Mexican patients with breast cancer selected by negative results in BRCA genes and age of early-onset diagnosis, identifying pathogenic variants in 6.4% (9.4% in those younger than 36

years). It also indicated that all patients identified with pathogenic variants had a family history suggestive of Li Fraumeni Syndrome (LFS), the youngest age at diagnosis was 24 years and the oldest age was 36 years.

George et al (2021), performed germline BRCA1, BRCA2, PALB2, and RAD51 genetic testing in a Caribbean population: 64% carried variants in BRCA1, 23% in BRCA2, 9% in PALB2, and 4% in RAD51C, CHEK2, ATM, STK11, and NBN. Of note, 9.0% of the deleterious variants were in PALB2, making it the highest rate of this variant in the world. Overall persons in the Bahamas had the highest proportion of hereditary breast and ovarian cancer (23%), followed by Barbados (17.9%), Trinidad (12%), Dominica (8.8%), Haiti (6.7%), Cayman Islands (6.3%) and Jamaica (4.9%).

Factors associated with hereditary breast cáncer

The risk of developing hereditary breast cancer is related to family history, mainly first-degree, and age at diagnosis. (Brewer et al., 2017).

Abugattas et al. (2015) studied the prevalence of BRCA 1/2 mutations in Peruvian women finding that 21% of patients were diagnosed before the age of 40 and 50.4% were diagnosed before the age of 50. They also found that the average age of diagnosis in women carrying a BRCA mutation was lower compared to non-carriers.

Villarreal-Garza, Alvarez-Gomez, et al., (2015) studied BRCA mutations using a Hispanic mutation panel, finding that 13% of cases possessed a mutation in BRCA genes and 92% were younger than 50 years. Likewise Cock-Rada et al. (2018) reported that BRCA gene mutation carriers had a mean age at diagnosis of 36 years.

Molecular diagnosis is a very important step in the clinical management of patients with breast cancer, as it allows the assessment of familiy history of breast cancer risk, the reduction of mortality, and the adoption of prophylactic measures, such as preventive mastectomy reducing the risk of cancer to up to 95% in BRCA1 / 2 carriers and other susceptibility genes. (da Costa et al., 2020)

Therefore, this first genetic study on breast cancer in Nicaragua aims to identify mutations associated with hereditary breast cancer, sequencing BRCA1/2, TP53, PALB2, CHECK2, ATM, and CDH1 genes, which will benefit families with genetic susceptibility, as well as propose to adjust the current standards of diagnosis and management of breast cancer in Nicaragua.

MATERIALS AND METHODS

An exploratory descriptive, cross-sectional and quantitative study was conducted between September and November 2016, in search of mutations in BRCA 1 and 2, Tp53, PALB2,

CDH1, PTEN, and CHEK2 genes in Nicaraguan women with histopathological diagnosis of breast cancer.

The universe consisted of 230 patients attended in the oncology area in three hospitals in Managua; Bertha Calderón Roque Hospital (Public), Solidaridad Hospital and Carlos Roberto Huembés Hospital (Social Security), 143 patients came from Bertha Calderón Hospital; 57 and 30 patients came from Solidaridad and Carlos Roberto Huembés Hospitals respectively.

The sample studied was 39 women (22 patients from the public hospital, 10 and 7 from the two social security hospitals) who met the inclusion criteria; having a diagnosis of breast cancer with or without family history who agreed to participate in the study. The type of sampling was non-probabilistic by convenience. The recruitment process of the participants began by using the registration databases of the hospitals, where the general data of the patients were obtained; from this data, telephone calls were made to invite the patients to a talk to inform them of the objective and benefits of the study.

The data source was primary, through the application of a clinical survey and the extraction of a blood sample. The study variables were: sociodemographic characteristics, personal and family aspects, and susceptibility genes. The survey was applied by the principal investigator and included sociodemographic variables, gynecological-obstetric history, and family history of cancer, among others. The sample collection and processing were carried out in the health sector laboratory of the Faculty of Medicine of the National Autonomous University of Nicaragua, UNAN-Managua by trained laboratory personnel. The peripheral blood sample was obtained through the vacuum system in a tube with EDTA anticoagulant.

Sample analysis: DNA extraction was performed following the QIAamp DNA Blood Mini Kit (QIAGEN) protocol which consists of four phases: a) Lysis of blood cells; b) Binding of genomic DNA to the QIAamp column membrane; c) Removal of residual contaminants; and d) Elution of pure genomic DNA. The concentrations and quality of extracted DNA (ratio 260nm/280nm, value ≥1.8) were evaluated using the NanoDrop spectrophotometer (Thermo Scientific lite). For sequencing, the Ion Torrent Personal Genome Machine (PGM) sequencer (Thermo Fisher Scientific, Waltham, MA, USA) was used. Sequence reads were mapped to the hg19 reference genome; and variants were predicted using both the Torrent Suite Variant Caller tool (TSVC, Thermo Fisher Scientific, Waltham, MA, USA) and the Genome Analysis Tool kit (GATK, Intel Corporation, Santa Clara, CA, USA). The sequencing process started with 30 ng of DNA, which was processed according to the standard Multiplex Ion AmpliSeq BRCA1 and BRCA2 Panel protocol (Life Technologies, Carlsbad, CA, USA). The panel amplifies 167 amplicons covering about 16.3 kb and resulting in 98-100% coverage of the coding regions of the genes. Libraries were designed according to the manufacturer by the Ion AmpliSeq Library Preparation

Protocol platform (Life Technologies, Carlsbad, CA, USA). Samples were barcoded and added to the emulsion and subsequently sequenced using a P1 chip. Each run of that protocol yielded approximately 10 Gb of data and each sample had an average depth of 500X.

To ensure the quality of the methodology applied during the process, from the extraction of the blood sample to obtaining the data, validation criteria and application of internal quality controls established in each technique or process were taken into account. First moment: Integrity of the extracted DNA; the purity of the DNA obtained from each of the samples was verified, as well as the integrity of the DNA was evaluated through the agarose gel electrophoresis run. Second moment: DNA sequencing carried out at the National Cancer Institute in the United States, where the Ion Torrent PGM parallel sequencing was used, which complies with the following parameters established to be valid:

1. Deep sequencing: with coverage of 160x, i.e. on average each base has been read more than 160 times, obtaining a margin of error of 0.01%.
2. Data filtering before processing: to eliminate sequence artifacts, before analysis, which can lead to erroneous conclusions. (Torrent Variant Caller 4.0)
3. Alignment: with the hg19 reference sequence by TMAP (also known as Homo_ sapiens_assembly19).

Results from patients carrying pathogenic variants were validated by subsequent capillary electrophoresis based on Sanger sequencing.

Data processing: Statistical programs such as SPSS version 21.0.0.0.0, and Microsoft Excel and Microsoft Word programs were used to process the variables sociodemographic characteristics and personal and family aspects. To calculate the frequency of the variables of interest, including genetic variables, once characterized, simple frequencies presented in tables were used. Bioinformatics tools, databases of the National Center for Biotechnology Information (NCBI) (ClinVar), Breast Cancer Information Core (BIC) that offer information on the relationship between the variants found and the cause of the disease were used to process and analyze the data obtained from the sequencing of the susceptibility genes and to determine their clinical significance. Additional variant analysis was performed using the Leiden Open Variation Database (LOVD) and ALIGN-GVGD, LOVD BRCA database, 2015.

The research protocol was endorsed by the Bioethics Committee of the Faculty of Medicine of the UNAN Managua. Once the patients were informed about the study, those who agreed to participate in the study signed a letter of informed consent, where they are requested to donate 5ml of peripheral blood and the explanation of the confidentiality of their results. The

confidentiality of the information on the results was guaranteed by giving identification codes to the samples and maintaining the anonymity of the patients' names.

RESULTS

Sociodemographic data: The average age of the patients was 50 years (range 25-70 years), the most affected age group was 46-50 years, with 28.2%, followed by 51-55 years with 25.6%, 41-45 years with 17.9%, 56-60 years with 10.3%, 66-70 years with 7.7% and for the age range 25-30 years, 31-35 years, 36-40 years, 61-65 years with 2.6% respectively. Ninety-two percent were from urban areas and 8% from rural areas. Regarding marital status, 43.6% were married, 35.9% were single, in a union, and divorced with 7.7% respectively. Regarding the academic level, 48.7% had university studies, 15.4% had primary and secondary studies respectively, 10.3% had technical studies and 5.1% did not complete primary and secondary studies respectively. Regarding labor activity, 46.2% were formally employed, 28.2% were housewives and 25.6% worked in the informal employment sector.

Obstetric and gynecological history: 38.5% of the patients had menarche before the age of 12 years and 61.5% after the age of 12 years. Regarding gestational history, 89.7% had at least one gestation and 10.3% were nulligestas. 87.2% had at least one child and 12.8% did not report any.

Eighty-two percent had their first pregnancy between 20-29 years of age, 7.7% between 30-39 years of age, and 10.3% had no pregnancies.

Regarding the use of planning methods, 56.4% do not report using them and 43.6% used them (injection 17.9%, IUD 15.4%, oral contraceptives 7.7%), and condoms 2.6%.

Family history of breast cancer: Regarding the family history of breast cancer, 53.8% of the patients reported a family history of breast cancer and 46.2% did not. Of those who reported this history, 5.2% corresponded to first-generation relatives (mother), 20.4% to second-generation (sister), 17.9% to third-generation (aunt), and 10.3% to the fourth generation (cousin).

Genetic study

In the sequencing of the BRCA1, BRCA2, TP53, PALB2, CDH1, PTEN, and CHEK2 genes, 29 types of mutations were identified of which only 3 mutations were pathogenic variants (10.3%), the rest were of benign clinical significance, uncertain, variants that have not yet been reported in the databases and others with pathogenicity conflict (89.7%). (Table 1)

Table 1.

Frequency and type of identified genetic variants (n=39)

Gen	No.	%	Mutation	Description	Clinical Significance	Change in Protein	dbSNP
BRCA1	15	38	c.4837A>G (p.Ser1613Gly)	missense	Benign	S1613G	rs1799966
	15	38	c.3113A>G (p.Glu1038Gly)	SNP	Benign	E1038G	rs16941
	4	10	c.3083G>A (p.Arg1028His)	SNP	Benign	R1028H	rs80357459
	2	5	c.2077G>T (p.Asp693Tyr)	missense	Benign	D693N	rs4986850
	1	2.5	c.3022A>G (p.Met1008Val)	missense	Benign	M1008V	rs56321129
	1	2.5	c.2002C>T (p.Leu668Phe)	missense	Benign	L668F	rs80357250
	23	59			Unrecorded	P824L	
	15	38			Unrecorded	K887R	
	1	2.5			Unrecorded	R1516K	

Gen	No.	%	Mutation	Description	Clinical Significance	Change in Protein	dbSNP
BRCA2	1	2.5	c.10249T>C (p.Tyr3417His)	NSP	Pathogenicity conflict	Y3417H	rs535952730
	1	2.5	c.467A>G (p.Asp156Gly)	NSP	Pathogenicity conflict	D156G	rs68071147
	1	2.5	c.1799A>T (p.Tyr600Phe)	NSP/ Missense	Uncertain Meaning	Y600F	rs397507276
	1	2.5	c.7534C>T (p.Leu2512Phe)	NSP	Pathogenicity conflict	L2512F	rs80358980
	11	28	c.1114A>C (p.Asn372His)	NSP/ Missense	Benign	N372H	rs144848
	10	26	c.865A>C (p.Asn289His)	NSP	Benign	N289H	rs766173
	10	26	c.2971A>G (p.Asn991Asp)	NSP/ Missense	Benign	N991D	rs1799944
	6	15	c.7469T>C (p.Ile2490Thr)	NSP	Benign	I2490T	rs11571707
	6	15	c.8851G>A (p.Ala2951Thr)	NSP	Benign	A2951T	rs11571769
	1	2.5	c.8830A>T (p.Ile2944Phe)	NSP	Benign	I2944F	rs4987047
	1	2.5	c.10234A>G (p.Ile3412Val)	NSP/ Missense	Benign	I3412V	rs1801426
	39	100			Unrecorded	V2446A	
	2	5	c.2808_2811del4 (p.Ala938Profs)	4pb Deletion	Pathogenic	A938fs	rs80359351

Gen	No.	%	Mutation	Description	Clinical Significance	Change in Protein	dbSNP
PALB2	2	5			Unrecorded	E67Q	
	1	2.5	c.629C>T (p.Pro210Leu)	SNP	Pathogenic Conflict	P210L	rs57605939
	1	2.5	c.1010T>C (p.Leu337Ser)	SNP		L337S	rs45494092
	8	20.5	c.1676A>G (p.Gln559Arg)	SPN	Benign	Q559R	rs152451
	2	5	c.2993G>A (p.Gly998Glu)	SPN	Benign	G998E	rs45551636
	1	2.5	c.2748+1G>T	SNP	Pathogenic	Not specified	rs753153576
TP53	1	2.5	c.524G>A (p.Arg175His)	SNP	Pathogenic	R175H	rs28934578

Source. Gene sequencing results

BRCA1: a total of 9 mutations corresponding to 31% (9/29) were identified; 20.6% were benign (S1613G, E1038G, R1028H, D693N, M1008V, and L668F) and 10.3% unrecorded (P824L, K887R, and R1516K). (Table 1)

BRCA2: a total of 13 mutations corresponding to 44.6% (13/29); 24. 1% were benign (N372H, N289H, N991D, I2490T, A2951T, I2944F and I3412V), 10.3% with pathogenicity conflict (Y3417H, D156G and L2512F), 3.4% were uncertain (Y600F), 3.4% unrecorded (V2446A) and another 3.4% were pathogenic (c.2808 _2811del4 (p. Ala938Profs) found in 2/39 (5%) of patients who had developed cancer at ages 44 and 46 years respectively and with family history. (Tables 1 and 2)

PALB2: A total of 6 mutations corresponding to 20.6%(6/29); 6.8% were benign (Q559R and G998E), another 6.8% with pathogenicity conflict (P210 and L337S), 3.4% not recorded (E67Q) and 3.4% was pathogenic (c.2748+1G>T). The patient carrying this mutation was diagnosed at 54 years of age and had a fourth-degree relative who had developed this same cancer (cousin) and another relative with another type of cancer. (Tables 1 and 2)

TP53: a mutation corresponding to 3.4% (1/29) was found; the pathogenic variant c.524G>A (p. Arg175His) was identified in one patient (1/39) diagnosed at 51 years of age with a history of this cancer and other cancers in the family. (Tables 1 and 2)

No mutations were identified in CDH1, PTEN, and CHEK2 genes.

Table 2.

Frequency and type of pathogenic mutations.

Gen	Number	%	Mutation	Change in protein	Age at diagnosis	Family history	Other familial cancers
BRCA2	1	2.5	3036delACAA	A938fs	46	2(Mother and aunt)	——-
BRCA2	1	2.5	3036delACAA	A938fs	44	2(Mother and aunt)	——-
PALB2	1	2.5	c.2748+1G>T	Not specified	54	1(Cousin)	Stomach (Nephew)
TP53	1	2.5	524G>A (p. Arg175His)	R175H	51	1(Aunt)	Prostate (Dad) Stomach (Aunt)
TOTAL	4/39	10	—	—	—	—	—

Source: gene sequencing results.

DISCUSSION

In this first study conducted in Nicaragua, we identified 10.2% (4/39) of women carrying pathogenic mutations, a proportion located in the range between 8% and 14% reported by other studies of families with hereditary breast cancer in Latin America and The Caribbean. (Vaca-Paniagua et al., 2012), (Villareal-Garza, Aguila et al., 2013) and 5-10% reported worldwide (Narod, S., & Rodriguez, A, 2011; Apostolou, & Fostira, F. 2013).

The variant identified in the BRCA2 gene (3036delACAA) is one of the six most frequent mutations among Latin American women (Jara et al., 2017), it is the most frequent in Europe and one of the ten most frequent worldwide (Rebbeck et al., 2018). Like

Abugattas et al., (2015) it was the only mutation identified in the BRCA2 gene in two Peruvian patients.

The characteristics of patients carrying the mutation in BRCA2, coincide with what is reported in the literature for breast cancer types of hereditary origin in which carriers of these mutations develop cancer at an earlier age, usually younger than fifty years (Fernández, A & Reigosa, A. 2016) and have more than one relative (first and/or second degree) affected with the same disease (Villarreal, Álvarez, et al., 2015; Abugattas et al., 2015, Brewer et al., 2017, Cock-Rada et al., 2018).

Regarding the mutation found in the PALB2 gene in a patient, it is similar to that reported in Colombia by Cock-Rada et al., (2018); in which they evidenced the importance of analyzing other breast cancer susceptibility genes (non-BRCA) in high-risk women, by observing a low frequency of founder mutations in BRCA1/2 genes (1.2%), and finding mutations in other genes such as PALB2, ATM, MSH2, and PMS2. Different studies have shown that the characteristics of patients carrying mutations in non-BRCA genes vary concerning the age at diagnosis, family history, and aggressiveness of the disease. As demonstrated by Adaniel et al., (2019); in their study, they identified four patients carrying mutations in the PALB2 gene, however, all of these patients had varied ages at diagnosis and family history.

The mutation found in the Tp53 gene (c.524G>A, p. Arg175His), in one patient in our study is similar to the three variants reported in Mexico by Gallardo-Alvarado et al., (2019), who analyzed patients negative for BRCA genes and who, like our patient, had a history of first, second and third-degree family history of breast cancer neoplasia, suggestive of LFS syndrome. Carraro et al., (2013) also reported a carrier patient with this same type of mutation, in a study performed in Brazilian women.

Genetic testing for BRCA genes and other breast cancer susceptibility genes is of great relevance for women with a family history, for individual and family preventive reasons, and therapeutic reasons for patients.

Despite their importance, Nicaraguan women still do not have access to genetic screening for pathogenic variants in those patients with a history of hereditary breast cancer. The country's situation is common to many low-resource countries as stated by Vaca-Paniagua et al., (2012) and Zabala et al., (2019).

As also indicated by da Costa et al., (2020) molecular diagnosis is essential for prophylaxis, clinical management, family risk assessment, and mortality reduction, especially for carriers of BRCA1 / 2 and other susceptibility genes.

CONCLUSION

These results reveal the need and importance of including molecular diagnosis in Nicaraguan patients at risk of developing breast cancer of hereditary origin, for their welfare and that of their families, achieving an early diagnosis, improving therapy and follow-up. Therefore, we recommend the integration of genetic screening for Nicaraguan women at risk of developing this disease and those who already have it.

It is important to study the variants of uncertain clinical significance and those of pathogenicity conflict, because their clinical significance may change if their relationship with this pathology becomes evident.

It is necessary to continue with genetic studies on hereditary breast cancer in Nicaraguan women and in countries where the prevalence and types of mutations are unknown. This will contribute to determining the mutational spectrum in BRCA 1/2 genes and other breast cancer predisposition genes, since the diversity and frequency of mutations in these genes among Latin American women are not clear, which limits the use of gene panels.

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