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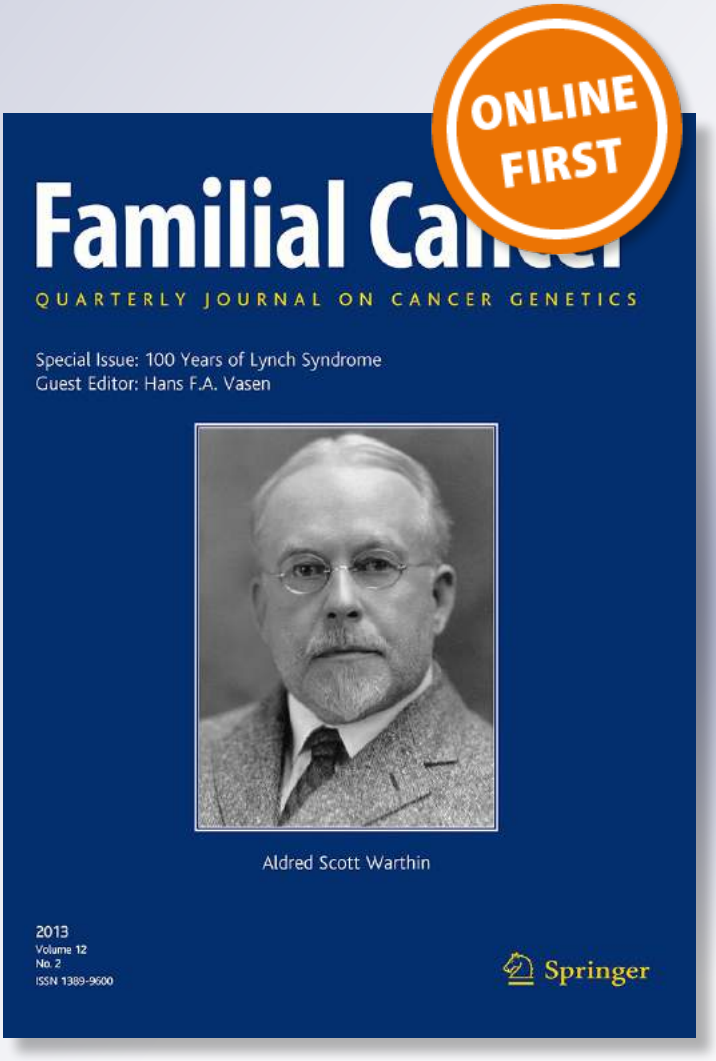
Familial Cancer

ISSN 1389-9600

Familial Cancer
DOI 10.1007/s10689-017-0004-z



Springer

Familial Cancer
DOI 10.1007/s10689-017-0004-z

ORIGINAL ARTICLE

A multi-gene panel study in hereditary breast and ovarian cancer in Colombia

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Abstract Germline mutations in BRCA1 and BRCA2 account for approximately 50% of inherited breast and ovarian cancers. Three founder mutations in BRCA1/2 have been reported in Colombia, but the pattern of mutations in other cancer susceptibility genes is unknown. This study describes the frequency and type of germline mutations in hereditary breast and/or ovarian cancer genes in a referral cancer center in Colombia. Eighty-five women referred to the oncogenetics unit of the Instituto de Cancerologia Las Americas in Medellin (Colombia), meeting testing criteria for hereditary breast and ovarian cancer syndrome (NCCN 2015), who had germline testing with a commercial 25-gene hereditary cancer panel, were included in the analysis. Nineteen patients (22.4%) carried a deleterious germline mutation in a cancer susceptibility gene: *BRCA1* (7), *BRCA2* (8), *PALB2* (1), *ATM* (1), *MSH2* (1) and *PMS2* (1). The frequency of mutations in BRCA1/2 was 17.6%. One BRCA2 mutation (c.9246dupG) was recurrent in five non-related individuals and is not previously reported in the country. Seventeen mutation-carriers had a diagnosis of breast cancer (median age of diagnosis of 36 years) and two of ovarian cancer. All BRCA1 mutation-carriers with breast cancer had triple negative tumors (median age of diagnosis of 31 years). Variants of unknown significance were reported in 35% of test results. This is the first report of a multi-gene study for hereditary breast and/or ovarian cancer in a Latin American country. We found a high frequency and a wide spectrum of germline mutations in cancer susceptibility genes in Colombian patients, some of which were not previously reported in the country. We observed a very low frequency of known Colombian founder BRCA1/2 mutations (1.2%) and we found mutations in other genes such as *PALB2, ATM, MSH2* and *PMS2*. Our results highlight the importance of performing multi-gene panel testing, including comprehensive BRCA1/2 analysis (full gene sequencing and large rearrangement analysis), in high-risk breast and/or ovarian cancer patients in Colombia.

Keywords Hereditary breast and/or ovarian cancer · Multi-gene cancer panels · BRCA1 · BRCA2 · Latin America · Hispanic

Introduction

Hereditary cancers represent 5–10% of all cancer cases [1]. The best studied hereditary cancer syndrome is hereditary breast and ovarian cancer (HBOC), which is caused by germline mutations in the BRCA1 and BRCA2 genes, transmitted in an autosomic dominant manner. BRCA1 and BRCA2 mutations are responsible for 30–50% of inherited breast and ovarian cancers [2–4]. In recent years, rapid advance in sequencing technologies has unveiled new susceptibility genes for breast and ovarian cancer [2]. However, some of these genes don't have management guidelines or established testing criteria. According to the national comprehensive cancer network (NCCN) guidelines, multi-gene panel testing is an option when more than one gene could be responsible for the patient's and/or family's cancer phenotype [5].

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Published online: 20 May 2017

Colombia, like many developing countries, has limited health care resources and most genetic tests have to be sent abroad at a high cost for the health care system. Therefore, patients without economic means, who really have an indication for genetic testing to rule out a hereditary cancer syndrome, are usually denied these tests. An alternative, less expensive approach to study *BRCA1/2* genes in certain populations has been to develop screening tests for founder and recurrent mutations specific to a population, and if negative, a comprehensive analysis of both genes (full gene sequencing and large rearrangement analysis) is performed [6, 7]. This strategy has proven cost-effective in populations such as Ashkenazi Jews, where 1/40 people are carriers of one of three founder mutations (185delAG, 5382insC, and 6174delT). Several European and non-European populations have also been found to carry specific founder mutations, although at a lower frequency [6, 8]. In Colombia, three founder mutations were observed and confirmed by haplotype analysis in unrelated families: 3450 delCAAG and A1708E in *BRCA1* and 3034 delACAA in *BRCA2* in Bogota [9]. However, there are limited studies of the prevalence of these mutations in different regions of the country. In Medellin (Antioquia province), a very low frequency (2%) of *BRCA1/2* founder mutations (2/244) was found in unselected breast cancer patients [10]. Admixture mapping studies have shown that Colombia has great heterogeneity in the ancestral genetic makeup among its different regions [11, 12]; therefore we expect different mutations in *BRCA1/2* to be found in different parts of the country. A better characterization of the *BRCA1/2* mutations throughout the country is needed in order to develop a cost-effective genetic testing strategy. Regarding mutations in other cancer-predisposing genes, there is no information about their prevalence in breast and ovarian cancer patients in Colombia or in other Latin American countries, since studies have mainly focused on *BRCA1/2* mutations in different Hispanic populations [7, 8, 13, 14].

The aim of this study was to describe the frequency and type of germline pathogenic mutations in breast and ovarian cancer susceptibility genes in patients with clinical criteria of hereditary breast and ovarian cancer syndrome, referred to the oncogenetics unit of the comprehensive cancer center, Instituto de Cancerologia Las Americas (IDC) in Medellin (Colombia), which serves a population of 4 million inhabitants and is a referral cancer center from the Province of Antioquia and other parts of the country.

Methodology

A retrospective analysis was performed of all patients with breast and/or ovarian cancer who were referred to the oncogenetics service of the Instituto de Cancerologia Las Americas in Medellin (Colombia), between February 2015 and August 2016, who underwent genetic testing with a 25-gene hereditary cancer panel. All patients included in the study fulfilled criteria for HBOC testing according to the NCCN guidelines: genetic/familial high-risk assessment: breast and ovarian, version 2, 2015 [5]. Patients had been tested through their health insurances for germline mutations in blood samples using a commercial 25-gene hereditary cancer panel (myRisk, Myriad), which included full sequencing and large rearrangement analysis of BRCA1, BRCA2, APC, ATM, BARD1, BMPR1A, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11 and TP53 and large rearrangement analysis of EPCAM. All patients had received pre and post-test genetic counseling at IDC. This descriptive case series study was approved by the independent ethics committee of the Instituto de Cancerologia Las Americas.

Statistical analysis of quantitative data was performed using Stata v12.0. The comparison of the age of diagnosis between mutation and non-mutation carriers was performed with the Student's t-test. Results were considered statistically significant at a p-value of 0.05 or less.

Results

Germline mutations in cancer-predisposing genes

Eighty-five patients with breast and/or ovarian cancer referred to the oncogenetics consultation of the IDC (Medellin, Colombia), were tested using a 25-gene panel to rule out a hereditary breast and/or ovarian cancer syndrome in the period between February 2015 and August 2016. Nineteen (22.4%) patients carried a deleterious mutation in a cancer-predisposing gene: seven in *BRCA1*, eight in *BRCA2*, one in *PALB2*, one in *ATM*, one in *MSH2* and one in *PMS2* (Table 1). We found five different *BRCA1* and four different *BRCA2* mutations in unrelated families (Table 1). Only one mutation (1.2%) was a known Colombian founder mutation (*BRCA1*: c.5123C > A (A1708E)), and most of the mutations were not previously reported in Colombian patients, including the *BRCA2* mutation, c.9246dupG, which was recurrent in five non-related individuals (Table 1). We also report the first *BRCA2* large rearrangement in Colombia. Interestingly this mutation has been previously observed in patients of Spanish origin [15].

We also found pathogenic germline mutations in the genes *PALB2, ATM, MSH2* and *PMS2*, not previously reported in Colombia. The *ATM* variant, c.43del, is a novel mutation not reported in the ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) database and is predicted to result in

Table 1 Germline mutations in breast and ovarian cancer in colombian patients

Mutation (HGVS nomenclature)	Mutation (BIC nomenclature)	Number of families	Previously reported in Colombia	Published
BRCA1				
c.213-12A>G	IVS5-12A>G	2	No	ClinVar[a]
c.68_69del AG	185delAG	1	No	ClinVar[a]
c.1674del	1793delA	2	Yes	Ovarian cancer in Colombia[b]/ClinVar[a]
c.5123C>A	A1708E	1	Yes	Colombian founder Mutation[c]/ClinVar[a]
c.3770_3771del	3889delAG	1	No	ClinVar[a]
BRCA2				
del exons 15-16		1	No	Spain[d]
c.5616-5620delAGTAA	5844del5	1	No	ClinVar[a]
c.9246dupG	9474insG	5	No	ClinVar[a]
c.6024dupG	6252insG	1	Yes	Ovarian Cancer in Colombia[b] / ClinVar[a]
PALB2 c.1240C>T		1	No	ClinVar[a]
ATM c.43del		1	No	No
MSH2 c.1552C>T		1	No	ClinVar[a]

[a] https://www.ncbi.nlm.nih.gov/clinvar/

[b] [18]

[c] [9]

[d] [15]

the premature truncation of the ATM protein at amino acid position 15 (p.Leu15*).

Clinical characteristics of germline mutation-carriers

All patients included in the study fulfilled criteria for HBOC genetic testing (NCCN Guidelines 2015). Seventy-eight patients had a personal history of breast cancer, six of ovarian cancer and one of breast and ovarian cancer (data not shown).

Seventeen mutation-carriers had a personal history of breast cancer, with a median age of diagnosis of 36 years (SD 6; range 28–48 years; Table 2). The median age of diagnosis of breast cancer in non-mutation carriers was 41 years (SD 11.3; range 17–63 years; data not shown). There was no significant difference in the age of diagnosis of breast cancer between mutation and non-mutation carriers ($p = 0.07$ [95% CI −59–10.73]). The mutation rate in breast cancer patients only was 21.5% (data not shown). Two mutation-carriers (*BRCA1* and *MSH2*) had a personal history of ovarian cancer (Table 2). The only patient with both breast and ovarian cancer was not found to carry a deleterious mutation.

The frequency of mutations in *BRCA1/2* in our patients was 17.6% (15/85). All of the *BRCA1* mutation-carriers with breast cancer had triple negative tumors, with a median age of diagnosis of 31 years (range 28–39 years). Interestingly, the only two mutations previously reported in Colombia (1793delA and A1708E), one of which is a founder mutation, were found in patients not born in Medellin or in the Antioquia province (Table 2). All *BRCA2* mutation-carriers had breast cancer, diagnosed at a median age of 38.5 years (range 31–43 years), with positive estrogen and progesterone receptor (HR+) tumors, and one with positive human epidermal growth factor receptor-2 (HER2+). Of note, most of the *BRCA2* mutation-carriers had family history of other cancers besides the HBOC cancer spectrum (i.e. breast, ovarian, prostate, pancreas, skin). The five patients with the *BRCA2* mutation, c.9246dupG, were all born in the province of Antioquia and some of their families had notorious family history of gastrointestinal tumors (one family had seven cases of gastric cancer) (Table 2). The large rearrangement in the *BRCA2* gene, a deletion of exons 15–16, was observed in a patient originally from the northern part of the Country (Fig. 1).

The two patients carrying a mutation in *PALB2* and *ATM* were diagnosed with breast cancer at age 36 and 48 years, respectively. Both patients had family history of breast cancer, but the *ATM* mutation carrier had a family history of other tumors not usually related to *ATM* heterozygous germline mutations (Table 2).

To our surprise we found a *PMS2* mutation in a patient with breast cancer diagnosed at age 31. Germline mutations in this gene cause hereditary non-polyposis colorectal cancer syndrome (HNPCC), also known as Lynch syndrome. The patient did not fulfill Amsterdam I or II criteria, but

Table 2 Clinical and histopathologic characteristics of patients with a germline mutation and breast or ovarian cancer

Patient no.	Mutation	Tumor type	Age of diagnosis	Family history	City of origin (province)
1	BRCA1: c.213-12A>G (IVS5-12A>G)	TNBC (IMC)	30	1FDR rectal	Medellín (Antioquia)
2	BRCA1: c.213-12A>G (IVS5-12A>G)	TNBC (DCIS, LCIS)	39	1SDR pancreas, 1SDR Gastric	Medellín (Antioquia)
3	BRCA1: c.68_69del AG (185delAG)	TNBC bilateral (IMC, IDC)	29	1FDR BC	Turbo (Antioquia)
4	BRCA1: c.1674del (1793delA)	TNBC (IDC)	32	No. adopted father	Ocaña (Norte de Santander)
5	BRCA1:c.5123C>A (A1708E)	TNBC (IDC)	28	No cancer history. Limited information	Barranquilla (Atlantico)
6	BRCA1:c.3770_3771del (3889delAG)	TNBC (IDC)	29	1FDR BC, 2FDR BC, 2TDR BC, 1TDR prostate	Medellín (Antioquia)
7	BRCA2 del exons 15-16	BC, HR+, Her2− (ILC)	41	3FDR BC, 1FDR esophagus, 1FDR thyroid, 1SDR OV and uterine, 3TDR prostate, 1TDR BC	Colosó (Sucre)
8	BRCA2: c.5616-5620delAGTAA (5844del5)	BC, HR+, HER2− (IDC)	35	Paternal: 2SDR leukemia, 1SDR prostate, 1TDR osteosarcoma. Maternal: 1DR BC and OV, 1SDR prostate, 1SDR lung, 1TDR esophagus	Medellín (Antioquia)
9	BRCA2: c.9246dupG (9474insG)	Bilateral BC, HR+, HER2+ (IDC)	41	3FDR BC, 2FDR gastric, 1FDR rectal, 2SDR gastric, 3TDR gastric, 3TDR BC	Medellín (Antioquia)
10	BRCA2: c.9246dupG (9474insG)	Bilateral BC, HR+, HER2− (IDC, DCIS)	39	1SDR prostate, 1TDR lung. Limited paternal history	Fredonia (Antioquia)
11	BRCA2: c.9246dupG (9474insG)	BC, HR+, HER2− (IDC)	35	4SDR uterine, 1 SDR liver. Limited paternal history	Medellín (Antioquia)
12	BRCA2: c.9246dupG (9474insG)	BC, HR+, HER2− (IDC)	43	1FDR OV. Limited paternal history	Medellín (Antioquia)
13	BRCA2: c.9246dupG (9474insG)	BC, HR+, HER2− (IDC)	31	Paternal: 1SDR BC, 1TDR BC, 2SDR gastric, 1TDR lung. Maternal: 1FDr BC, 1DR BC, 1SDR pancreas	Medellín (Antioquia)
14	BRCA2 c.6024dupG 6252insG	BC, HR+, HER2− (IDC)	43	Paternal: 1FDR prostate, 1SDR prostate, 2 TDR prostate. Limited maternal history	Cali (Valle)
15	PALB2 c.1240C>T	BC, HR+, HER2− (IDC)	36	Paternal: 1SDR BC, 1TDR BC. Maternal: 1SDR sarcoma, 1SDR colon	Medellín (Antioquia)
16	ATM: c.43del	BC, HR+, HER2− (IDC)	48	1FDR BC, 1SDR OV, 1SDR leukemia, 2SDR gastrointestinal, 1TDR brain	Medellín (Antioquia)
17	PMS2: c. 137G>T	BC, HR-, HER2+ (IDC)	31	Paternal: 1SDR BC, 1SDR OV/uterine, 1SDR thyroid, 1SDR leukemia, 1SDR colon, 1TDR pancreas, 1TDR liver, 1TDR lymphatic. Maternal: 1FDR ear, skin, 1SDR BC, 1SDR BC, skin, 1TDR Leukemia	Medellín (Antioquia)
18	BRCA1 c.1674del (1793delA)	Bilateral OV (serous)	47	1FDR OV, 1SDR BC, 2TDR BC, 1TDR Lung	Ibagué (Tolima)
19	MSH2 c.1552C>T	OV (Clear cell)	58	1FDR OV and Ileum, 1FDR uterine, 1FDR tongue, 1FDR colon and kidney, 1SDR BC, 1SDR colon, 2TDR colon, 1TDR gastric and throat	Bello (Antioquia)

BC breast cancer, *TNBC* triple negative breast cancer, *IDC* invasive ductal carcinoma, *IMC* invasive medullar carcinoma, *DCIS* ductal carcinoma in situ, *LCIS* lobular carcinoma in situ, *HR* hormone receptors (estrogen receptor, progesterone receptor), *HER2* human epidermal growth factor receptor 2, *FDR* first degree relative, *SDR* second degree relative, *TDR* third degree relative, *OV* ovarian cancer

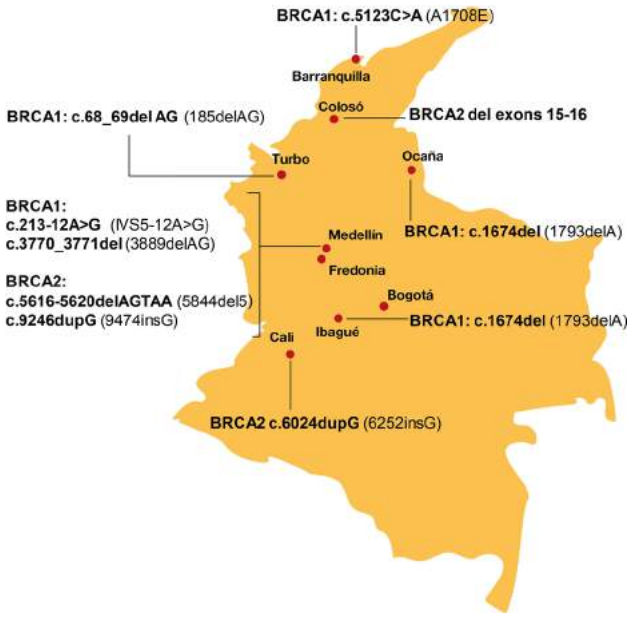

Fig. 1 Origin of BRCA1/2 mutation carriers (Colombian map)

she had a family history of some Lynch-related tumors [16, 17]. This particular mutation is published in ClinVar as being pathogenic or likely pathogenic in Lynch and Turcot syndrome (https://www.ncbi.nlm.nih.gov/clinvar/).

One of the patients with the *BRCA1* mutation, c.1674del (1793delA), had a diagnosis of bilateral ovarian cancer (serous type) at 47 years old, and a family history of breast and ovarian cancer (Table 2). This mutation was already reported in a series of ovarian cancer patients in Colombia [18].

The patient with ovarian cancer and the *MSH2* mutation met criteria for HBOC testing, but her family history was more suggestive of a Lynch Syndrome (Table 2). There is limited information about Lynch syndrome in Colombia and this is a novel mutation in the country.

Variants of unknown significance (VUS)

We found a frequency of 35% of variants of unknown significance (VUS) in one or two genes in this 25-gene panel (Table 3). Only three VUS in *BRCA1/2* (3.5%) were present in these patients. Some variants were present in more than one individual (PMS2, BARD1, RAD51C). The variant PMS2 (c.2395C > T or R799W) was present in four unrelated patients.

Discussion

We observed a frequency of 22.4% of germline mutations in breast and/or ovarian cancer patients meeting NCCN genetic testing criteria, using a 25-gene panel for Hereditary Cancers. There are no prior reports in Latin America of multi-gene analyses beyond *BRCA1* and *BRCA2* in breast and ovarian cancer patients, in order to compare the mutation frequency we observed in our population. We found a frequency of *BRCA1/2* mutations of 17.6%, which is similar to other studies in Hispanic populations in breast and ovarian cancer patients selected for family history and/or age of diagnosis [9, 13, 19–22]. There are many publications that show wide differences in *BRCA1/2* mutation frequencies in breast and/or ovarian cancer in Hispanic patients, which is mainly due to the difference in patient selection criteria, the techniques used to analyze these genes (full gene sequencing and large rearrangement studies vs. mutation panels or incomplete *BRCA1/2* testing), as well as differences in the genetic background of the studied populations. Many of these studies have been done in Hispanics residing in the US, which are mainly of Mexican origin [21–24].

Regarding the clinical and histopathologic characteristics, we found a very young mean age of diagnosis, 31 years, of breast cancer in *BRCA1* mutation carriers as compared with the study published by Lagos-Jaramillo et al. that found a median age of diagnosis of breast cancer of 36.9 years in Hispanic *BRCA1* mutation carriers (80% Mexican ancestry) [25]. We also found that 100% of our *BRCA1* mutation carriers had triple negative tumors as compared to 74% in the same study [25]. Hispanics or Latin Americans throughout the continent are usually analyzed as the same ethnic group; however, admixture mapping studies have shown great genetic heterogeneity across Latin American countries and even within the same country, such as Colombia [11, 12, 26]. In our study we found different mutations in patients born in different regions of the country, which could be explained by the diverse genetic makeup of Colombia. We also observed a very low frequency of known Colombian founder mutations (1.2%) in the studied population and a frequency of 7% (1/15) among *BRCA1/2* mutation carriers compared to 77% (10/13) reported by Torres et al. in Bogota [9]. Since the discovery of the three *BRCA1/2* founder mutations, a commercial 6-mutation panel test, the "Colombian profile", was developed to study these three mutations and other three recurrent mutations reported in studies performed in Bogota. Until recently, this was the only *BRCA1/2* test covered by the health care system in Colombia, which led to incomplete BRCA testing with inaccurate counseling and management of families. Our study demonstrates the low clinical utility of testing only these selected mutations. Even though we found recurrent mutations and a possible founder mutation in the Antioquia population (haplotype analysis are needed to confirm this), we observed a wide spectrum of mutations in patients born in different regions of the country, including a large rearrangement in *BRCA2*,

Table 3 Variants of unknown significance (VUS)

VUS (HGVS nomenclature)	Deleterious mutation
BRIP1 c.3079G>A	No
APC c.5017G>A MSH6 c.2906A>C	No
ATM c.1703G>T CDKN2A c.-2G>A	No
PMS2 c.2395C>T	No
CDKN2A c.217A>C PMS2 c.241G>A	No
BARD1 c.33G>T	No
MLH1 c.2213G>A	No
ATM c.1444A>C PMS2 c.2395C>T	No
ATM c.5039C>T NBN c.1222A>G	No
BRIP1 c.2220G>T	No
BARD1 c.33G>T	No
RAD51C c.492T>G	No
PALB2 c.23C>T	No
BRIP1 c.790C>T	No
TP53 c.173C>G	No
MSH2 c.2684C>T	No
APC c.8430T>A NBN c.2150C>T	No
PMS2 c.2395C>T	No
BRCA1 c.1181G>T APC c.6958C>T	No
MSH6 c.4004A>C	No
NBN c.456G>A	No
BRCA2 c.324T>A	No
PALB2 c.483C>G	No
PMS2 c.1243G>A	No
MSH6 c.2419G>A	BRCA1 c.1674del (1793delA)
TP53 c.139C>T	BRCA1 c.213-12A>G
BRCA1 c.5408G>T	BRCA2 c.9246dupG (9474insG)
PMS2 c.2395C>T RAD51C c.492T>G	BRCA1 c.1674del (1793delA)
SMAD4 c.677C>T	BRCA2 c.5616-5620del (5844del5)
PMS2 c.241G>A	PALB2 c.1240C>T

supporting the need of performing a comprehensive analysis of both genes (full sequencing and large rearrangement test) in a clinical setting.

Most of the patients referred to the oncogenetics consultation in the IDC met more than one criteria for HBOC genetic testing, for example young age of diagnosis (breast cancer < 45), and family history (two or more breast/ovarian cancers); therefore, the probability of finding a mutation was higher than patients who fulfill only one criteria. All patients included in the study met criteria for HBOC genetic testing according to NCCN 2015 guidelines, but most of them also had a family history of cancers usually not characteristic of HBOC. Therefore, by testing other genes besides *BRCA1/2*, we found mutations in the genes *PALB2, ATM, MSH2* and *PMS2*, increasing the mutation detection rate by 5% compared to testing only *BRCA1/2*. This shows that a multi-gene panel study is a valid approach and may be more efficient in terms of time and costs than a stepwise single-gene approach in this setting, as is advised by the NCCN guidelines [5]. However, commercial multigene panel tests that include moderate and high penetrant genes for different hereditary cancer syndromes can lead to unexpected findings, such as the 31-year old breast cancer patient with a *MSH2* germline mutation. Genetic counseling and decision making in these cases can be more challenging.

A major limitation of testing moderate-penetrant genes for breast cancer, such as *ATM*, is the lack of treatment and follow-up guidelines. A recent update in the NCCN guidelines included more information on clinical management for some of these genes. However, most commercial laboratories tend to introduce more and more genes in their cancer panels with unknown or uncertain cancer risks and no evidence-based recommendations for management, just because the cost of sequencing is the same for one or several genes. Therefore, the best management in these cases is with a multidisciplinary team or within a clinical research protocol, as advised by NCCN guidelines.

A main disadvantage of multi-gene panels is that the rate of VUS increases considerably compared to a single-gene approach. For *BRCA1/2* alone, we found a VUS frequency of 3.5%, which increased to 35% with the study of 25 genes, and sometimes two VUS were found in the same patient. The literature reports a rate of VUS that ranges from 3.3 to 42% according to the lab and the number of genes tested [27]. To our surprise, our VUS rate was within this range, taking into account that our population is less studied than other populations; therefore we expected to find a higher VUS rate. This is the first report of the rate of VUS in a commercial cancer panel in our population.

For the reasons mentioned above, Genetic counseling offers great support to the treating doctors, the patient and their families, especially when ordering multi-gene panel tests. An expert in cancer genetics should interpret the genetic results. Genetic tests remain very expensive, even though costs are continuously going down and there are more options in the market every day. The choice of the laboratory should also be taken with extreme caution, since false positive or false negative test results could lead to wrong clinical management decisions or unnecessary prophylactic surgeries.

Conclusions

This is the first report of a multi-gene study for hereditary breast and/or ovarian cancer in a Latin American country. We found a high frequency (22.4%) and a wide spectrum of germline mutations in cancer predisposing genes (*BRCA1/2, PALB2, ATM, MSH2* and *PMS2)* in Colombian patients, some not previously reported in the country [5]. We observed a very low frequency of known Colombian *BRCA1/2* founder mutations (1.2%), suggesting that testing only founder mutations in our population is not a cost-effective strategy. We found a *BRCA2* mutation, not previously reported in our population, which could be a new founder mutation. Since Colombia is a country of great genetic heterogeneity, more extensive studies are needed in different regions to determine the real prevalence and spectrum of mutations in cancer-predisposing genes. Colombia has very high rates of breast cancer in women diagnosed under age 50, which could benefit from these genetic tests [28, 29]. Our results indicate that multi-gene panel testing, including *BRCA1/2* comprehensive analysis (full gene sequencing and large rearrangement analysis), is a valid approach in high-risk breast and ovarian cancer patients in Colombia.

Acknowledgements This study was supported and funded by the Instituto de Cancerologia Las Americas and the Comité para el Desarollo de la Investigación—CODI, CPT 1229, Universidad de Antioquia. We also thank the team of the Instituto de Cancerologia Las Americas: Dr. Mauricio Borrero, Dr. Fernando Herazo, Dr. Gonzalo A. Angel, Dr. Rene Pareja, Dr. Gabriel J. Rendon, Dr. Luis J. Palacios, Dr. Maria E. Montoya, Dr. Diego M. Gonzalez, Dr. Luz D. Suarez, Dr. Alejo Jimenez, Dr. Eduardo Gutierrez, Dr. Leon D. Ortiz, Dr. Pedro A. Reyes, Dr. Adolfo L. Lopez, Dr. Aminta Perez, Dr. Franz Usuga, Dr. Isabel C. Duque, Dr. Lina M. Arbelaez, Dr. Joaquin P. Rueda, Dr. David A. Mosquera, Paula Arboleda, Alejandra Saldarriaga, Adine Carvajal, Viviana Sanchez, Angela Estrada and Tatiana Gutierrez.

Authors contributions AMCR and AO drafted the manuscript. AMCR performed Genetic Counseling of the patients. All authors revised the article critically and approved the final manuscript.

Compliance with ethical standards

Conflict of interest AMCR received financial support from Gencell for attending the meeting "IARC 2016: Global Cancer, Ocurrence, Causes and Avenues to Prevention" in France and the "XIV Congreso Nacional y VIII Congreso Internacional de Genética Humana" in Colombia in 2016. The other co-authors declare that they have no conflict of interest.

Ethical approval All procedures performed involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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