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CLINICAL REPORT

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Population-based screening of Uruguayan Ashkenazi Jews for recurrent *BRCA1* and *BRCA2* pathogenic sequence variants

Cecilia Castillo[1] | **Nora Artagaveytia**[2] | **Lucia Brignoni**[2] | **Yael Laitman**[3] | **Natalia Camejo**[1] | **Ana Laura Hernández**[4] | **Gabriel Krygier**[1] | **Alfonso Cayota**[2,5] | **Lucia Delgado**[1] | **Eitan Friedman**[3,6]

[1]Servicio de Oncología Clínica, Hospital de Clínicas "Dr. Manuel Quintela", Facultad de Medicina, Universidad de la Republica, Montevideo, Uruguay

[2]Departamento Básico de Medicina, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

[3]The Susanne Levy Gertner Oncogenetics Unit, Institute of Genetics, Sheba Medical Center, Tel Hashomer, Israel

[4]Departamento de Psicología Médica, Hospital de Clínicas "Dr. Manuel Quintela", Facultad de Medicina, Universidad de la Republica, Montevideo, Uruguay

[5]Laboratorio de Genómica Funcional, Institut Pasteur de Montevideo, Montevideo, Uruguay

[6]The Department of Genetics and biochemistry, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Correspondence
Cecilia Castillo, Servicio de Oncología Clínica, Hospital de Clínicas "Dr. Manuel Quintela", Facultad de Medicina, Universidad de la República, Montevideo, Uruguay.
Email: cascecilia@gmail.com

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Abstract

In Ashkenazi Jews (AJ) three recurring pathogenic sequence variants (PSVs) are detected in ~2.5% of the general population in the *BRCA1* (c.68_69del = 185delAG, c.5266dup = 5382insC), and *BRCA2* (c.5946del = 6174delT). Population-based screening for these PSVs in AJ women is part of the health basket in Israel. To assess the feasibility and outcome of *BRCA* genotyping in the Jewish population of Uruguay, AJ in the greater Montevideo area were recruited using ethically approved protocol and without pretest counseling were genotyped for the three predominant AJ PSVs in the *BRCA* genes. Independently confirmed PSV carriers were counseled, and genetic testing was offered to additional family members. Overall, 327 participants were enrolled: 312 (95%) female, 261 (80%) had all four grandparents AJ, and 14 (4%) women were breast cancer survivors with a mean age ± standard deviation (SD) 50 ± 11.5 years. The *BRCA1* c.68_69del PSV was detected in three cancer free participants (0.92%, CI 95% 0.31–2.6), all with a suggestive family history. No carriers of the other two recurrent PSVs were detected. Online oncogenetic counseling was provided for all carriers. In conclusion, the rate of the *BRCA1* c.68_69del PSV was similar with the rate in other AJ communities. AJ population *BRCA* genotyping screens in Uruguay seem feasible and should be promoted.

KEYWORDS

Ashkenazi Jews, *BRCA1 BRCA2* genes, cancer risk, oncogenetic counseling, population-based genotyping

1 | INTRODUCTION

In Uruguay, breast cancer (BC) is the most frequent type of feminine cancer and the leading cause of cancer-related death in women (Uruguayan Honorary Commission to fight Cancer, 2020). About 5%–10% of BC develop in the context of hereditary cancer syndrome, with autosomal dominant inheritance pattern. BC (and ovarian cancer) predisposition syndrome is most commonly associated with germline pathogenic sequence variants (PSVs) in either the *BRCA1* (Ensembl:ENSG00000012048; MIM:113705; AllianceGenome:HGNC:1100; GENBANK NG_005905.2; NM_007924.4) or the *BRCA2* (Ensembl:ENSG00000139618; MIM:600185; AllianceGenome:HGNC:1101; GENBANK U43746.1; NM_000059) genes. *BRCA1* and *BRCA2* PSV carriers are at a cumulative BC lifetime risk of 72% for *BRCA1* and 69% for *BRCA2* (Kuchenbaecker et al., 2017). Moreover, *BRCA* PSV carriers are also increase risk for developing ovarian cancer, with a cumulative risk of 40%–45% for *BRCA1* and 15%–20% for *BRCA2* (Evans et al., 2008; Kuchenbaecker et al., 2017; Milne et al., 2008).

While in most outbred, genetically heterogeneous populations *BRCA1/BRAC2* PSVs are family specific, with 2228 and 2672 recorded unique PSVs in *BRCA1* and *BRCA2*, respectively (https://brcaexchange.org/factsheet), in some ethnic groups, a limited set of PSVs in both genes has been described: Polish, Icelandic, and Ashkenazi Jews (AJ) (Rebbeck et al., 2018). Among AJ in cancer free, unselected population, the rate of the recurring three PSVs in *BRCA1* (c.68_69del; p.Glu23fs; rs80357914 = 185delAG, c.5266dup; p.Gln1756fs; rs80357906 = 5382insC), and *BRCA2* (c.5946del; p.Ser1982fs; rs80359550 = 6174delT) is ~1 in 40 (2.5%) (Roa et al., 1996). Moreover, these three PSVs combined account for >90% of reported cases of hereditary breast and ovarian cancer in AJ (Rosenthal et al., 2015).

Population screening for *BRCA1/BRCA2* PSVs has been advocated for AJ, based on the results of several prospective studies that have shown this approach to be feasible, highly cost-effective, and importantly not associated with negative psychological or long-term quality-of-life effects (Gabai-Kapara et al., 2014; Manchanda et al., 2017, 2020; Manchanda, Legood, et al.,). These population-based *BRCA* targeted screens were carried out in AJ residing primarily in Israel, the United Kingdom, and the United States. To what extent these efforts can be carried out and implemented in AJ populations residing elsewhere has not been well established, and the current study was focused on the AJ population of Uruguay.

2 | MATERIALS AND METHODS

2.1 | Participant identification and recruitment

Eligible individuals were offered participation in the study through publications in local Jewish community newspapers, informative talks, and an explanatory leaflet distributed during oral presentations of the study goals in Jewish community centers and synagogues in the greater Montevideo area. Individuals of any gender, aged ≥25 years, with at least one of the four grandparents (maternal or paternal) being of AJ ancestry, not previously genotyped for *BRCA1* and *BRCA2* PSVs, and no known *BRCA1* or *BRCA2* PSVs in the family were eligible. The protocol was approved by the Research Ethics Committee of the Hospital de Clínicas "Dr. Manuel Quintela.". All participants gave a written informed consent prior to study participation. Interested eligible participants signed an informed consent, completed a form with sociodemographic data that included personal and family history of cancer and age at cancer diagnosis. Of note, pretest genetic counseling was not offered.

2.2 | Genetic analysis

Saliva samples were collected, pseudo-anonymized and linkage with the identity of the participants was maintained in Uruguay and not transferred to the genetic testing laboratory. Samples were stored in a refrigerator until processing. DNA extraction was performed using the PureLink Genomic DNA Mini Kit (Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA). The samples were analyzed using a NanoDrop spectrophotometer to determine their concentrations and purity. The detection of the three recurrent PSVs was carried out at the Oncogenetics Unit of the Sheba Medical Center in Israel. The analysis was performed with the BRCA kit (Savyon Diagnostics Ltd.) using the NanoChip® NC400 automated microarray platform (Nanogen, San Diego, CA), as previously described (Schayek et al., 2016). PSV identified using the

array were confirmed in Uruguay with a new DNA sample extracted from blood, and analysis by conventional sequencing (Sanger) performed at MACROGEN (Seoul, Korea), Institut Pasteur de Montevideo, Uruguay, and Laboratorio Genia (Montevideo, Uruguay).

2.3 | Oncogenetic counseling

Genetic counseling for participants was carried out at the Oncogenetics Unit of the Clinical Hospital following standard guidelines and including those tested and first-degree relatives who were interested. Noncarriers who were considered high cancer risk based on well-accepted criteria, (National Comprehensive Cancer Network (NCCN), n.d.; https://www.cancer.org/cancer/cancer-causes/genetics/family-cancer-syndromes.html) were offered a subsequent genotyping platform using a multigene panel testing, or complete sequencing of *BRCA1* and *BRCA2*.

3 | RESULTS

3.1 | Participant characteristics

Between April and November 2018, 355 individuals were offered participation and 327 (92.1%) eligible individuals from 282 extended families [312 (95.4%) of whom women; mean age was 47 ± 12.9 years (SD); range 22–83 years)] were recruited. Of participating families in 229/282 (81.2%) all four grandparents were of Ashkenazi ancestry, 43 (15.2%) had two Ashkenazi grandparents, and two and eight families had three and one Ashkenazi grandparents, respectively. After signing the informed consent and filling a short questionnaire, saliva samples were obtained from all participants. in 261 (79.8%) all four grandparents were of AJ ancestry. Fourteen (4.5%) female participants had previously been diagnosed with breast cancer (mean age at diagnosis 50 ± 11.5 years (SD); range 32–65 years), and 82 (25%) had family history suggestive of having an inherited cancer predisposition. Relevant characteristics of the participants are shown in Table 1.

TABLE 1 Some relevant characteristics of study participants

Characteristic	No. of patients (*N* = 327)	%
Mean age (range) years	47 (22–83)	
Age category		
<40 yr	86	(26.3)
≥40to <60 yr	174	(53.2)
≥60 yr	67	(20.5)
Female sex	312	(95.4)
Level of education		
College	250	(76.4)
High school	63	(19.2)
Primary	1	(0.3)
No data	13	(4)
Ethnicity		
Four Ashkenazi grandparents	261	(79.8)
At least one Sephardic grandparent	34	(10.4)
At least one non-Jewish grandparent	11	(3.4)
At least one grandparent of unknown origin	8	(2.5)
No data	13	(3.9)
Previous cancer diagnosis in women—no. (%)		
Breast	14	(4.5)
Colon	3	(<1)
Previous cancer diagnosis in men—no. (%)		
Prostate	2	(13)
Personal and/or family history for suggestive of inherited cancer		
Yes	82	(15)
No	234	(80.6)
No data	11	(4.4)

3.2 | Genotyping data

Genotyping of the three recurrent AJ *BRCA* PSVs in Israel with the automated microarray platform and subsequent DNA sequencing of an independent DNA extortion from blood in Uruguay resulted in the confirmation of three unrelated female participants as carriers of the pathogenic *BRCA1* c.68_69del variant—a prevalence of 0.92% (CI 95% 0.31–2.6). No carriers of the two other recurrent PSVs were identified among study participants. Pedigrees of the carrier cases are shown in Figure 1a–c. Two of the three carriers had-two Ashkenazi grandparents and the third one—all four grandparents were of Ashkenazi origin.

3.3 | Genetic counseling

Posttest oncogenetic counseling was provided to all three carriers, at the oncogenetics service in Uruguay as well as video calls with the oncogenetics team in Israel. Genetic screening was also offered to (via the proband) first-degree relatives and performed in those who agreed, followed by subsequent genetic counseling. The results for

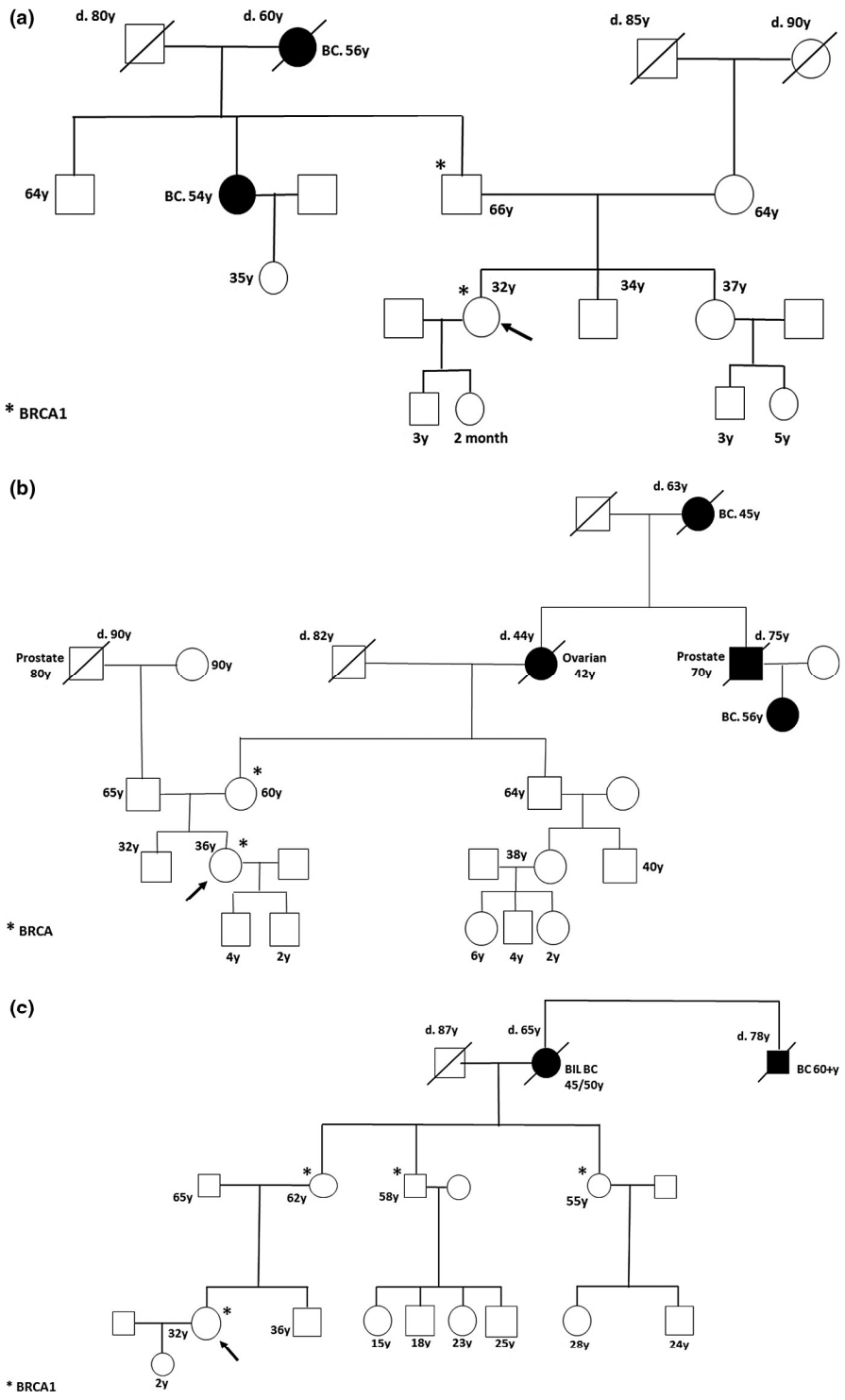

FIGURE 1 (a)–(c) Pedigrees of the carrier cases

this extended genotyping at the time of publication are also presented in Figure 1a–c.

4 | DISCUSSION

This is the first population-based study that genotyped the recurrent *BRCA1 BRCA2* PSVs in the Uruguayan Jewish mostly Ashkenazi population. The results of this study show that the rate of one of the three predominant AJ PSVs in these two genes is similar to that reported in AJ populations in other countries ~0.9% (Abeliovich et al., 1997; Bahar et al., 2001; Ferla et al., 2007). Previous Latin American based study reported the results of genotyping of these recurring PSVs in AJ women from Porto Alegre, Brazil, not selected for personal or family history of cancer. In that study, carrier rates for *BRCA1* c.68_69del and c.5266dup were 0.78% (2/255; 95%CI 0.10–2.8) and 0,

respectively, and 0.4% (1/255; 95%CI 2.45–8.08) for the *BRCA2* c.5946del (Dillenburg et al., 2012). Taken together with studies from other parts of the world that focused on that ethnic group (Israel, Canada, USA-summarized in Table 1 of reference [Dillenburg et al., 2012]) we can conclude that the rate of the c.68_69del *BRCA1* PSV is similar in all genotyped AJ communities (range 0.96%–1.14%). Notably the same sequence variant was also detected in non-AJ primarily Iraqi Jews (Bar-Sade et al., 1998) and in non-Jews as well. In some of these non-Jewish carriers (e.g., Hispanics living in the South West part of the United States (Makriyianni et al., 2005) and the San Francisco bay area) the haplotype indicates that they are ancestrally descendants of the Jewish community in Spain expelled in 1492 and moved to the new world (Velez et al., 2012). In non-Jewish individuals from West India and Malaysia the haplotype indicates that this PSV arose independently (Kadalmani et al., 2007; Laitman et al., 2013).

There were no carriers of the two other recurring PSVs, *BRCA1* c.5266dup and *BRCA2* c.5946del, which have a reported frequency in previous AJ population-based studies of 0.13%–0.28% and 0.6%–1.52%, respectively (Abeliovich et al., 1997; Bahar et al., 2001; Ferla et al., 2007; Gabai-Kapara et al., 2014; Manchanda et al., 2020). The most plausible explanation for the lack of detection of these PSVs is the small number of genotyped individuals and the fact that not all were "full AJ" as assigned by all four grandparents being AJ. In fact, ~20% of the participants in our study had at least one grandparent of non-Ashkenazi Jewish ancestry. Only an extended study that encompasses more AJ participants from Uruguay may be able to shed light on the reasons for the lack of detecting these two additional recurring PSVs in the current, preliminary study.

Although participant enrollment within the Uruguayan AJ community far exceeded our initial objective (100 expected participants vs. more than 300 enrolled), it would be of interest to carry out a subsequent survey targeting the entire Jewish community in Uruguay to determine the enrollment and acceptance rate of carrying out population-based genotyping and identify potential barriers to a more widespread implementation. In this context, it has previously been shown by Manchanda and coworkers (Manchanda et al., 2019) that having prior knowledge about the study, being married, having children, and believing that knowing the result decreases health-related uncertainty, are factors positively associated with the acceptance of oncogenetics testing. In the same study cancer risks concerns, study limitations (e.g., confidentiality, emotional impact, inability to prevent cancer, and stigmatization), as well as being male and having a lower education level were significantly associated with a lower likelihood of acceptance of *BRCA* testing (Damiani et al., 2015). Notably, 76% of current study participants have at least a college degree, confirming the known association between adhering to recommended health-related screening methodologies (e.g., breast and cervical cancer) and education levels (Damiani et al., 2015). One plausible implication is to facilitate population level education regarding the benefits of screening techniques for early detection of cancer, although this is speculative and not based on the actual results of the current study.

Of note, there was a paucity of male participants in the current study. Although this gender associated genetic testing uptake has been previously reported (Manchanda, Loggenberg, et al., 2014), we can only speculate as to the reasons for this observation: the fact that the personal risk for developing cancer in men *BRCA* PSV carriers is substantially lower than it is for women, the fact that breast cancer is a both perceived and is overwhelmingly a feminine disease may play a major role in the low number of male participants in *BRCA* population-based genotyping studies.

All posttest results disclosure sessions were done both in Uruguay and online, with an experienced oncogeneticist (EF) in Israel. The sessions lasted about 45 minutes and were handled with the use of an interpreter for those who do not master the English language. The feedback from these three sessions was positive, emphasizing some lessons that COVID-19 pandemic taught the medical community to expand the use of remote genetic counseling, including oncogenetics.

In conclusion, the rate of the most common AJ *BRCA1* PSV (c.68_69del = 185delAG) is similar in the Uruguayan mostly Ashkenazi Jewish community as in other AJ communities world-wide. The high enrollment rate is encouraging for expanding this preliminary study to more individuals of this ethnic origin in Uruguay. Moreover, the technological advantages enabling remote, posttest result disclosure on line, pave the way to an ongoing collaboration and exchange between Israeli and Uruguayan researchers focusing on hereditary cancer.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception and design: E Friedman, N Artagaveytia, C Castillo, L Delgado. Administrative support: N Artagaveytia, N Camejo, C Castillo, E Friedman. Provision of patients: all authors Collection and assembly of data: N Camejo, C Castillo, N Artagaveytia, L Brignoni, E

Friedman, Y Laitman. Data analysis and interpretation: all authors. Manuscript writing, final approval of manuscript, and agreement to be accountable for all aspects of the work: all authors.

ETHICS STATEMENT

The study was conducted in accordance with international ethical standards for biomedical research: MERCOSUR guidelines on the regulation of clinical trials, the Declaration of Helsinki, and the research regulations approved by the National Ethics Commission in 2019. Patient anonymity was maintained in the statistical analyses, and approval for this study was obtained from the Ethics Committee of Hospital de Clínicas.

DATA AVAILABILITY STATEMENT

All data available are presented herein.

ORCID

Cecilia Castillo https://orcid.org/0000-0002-0417-0512
Natalia Camejo https://orcid.org/0000-0002-8684-0291
Eitan Friedman https://orcid.org/0000-0002-6745-1733

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