Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Expanding BRCA1/BRCA2 genomic diversity in the Caribbean: insights from the first national cohort in the Dominican Republic

Noelia Parra
Referencia Laboratorio Clínico
Isabel C. Lucero
Referencia Laboratorio Clínico
Elizabeth Castell
Instituto Tecnológico de Santo Domingo (INTEC)
Marianna Figueroa
Referencia Laboratorio Clínico
Thais E. Reyes
Referencia Laboratorio Clínico
Eileen Riego
eileenr@labreferencia.com
Referencia Laboratorio Clínico

Research Article

Keywords: BRCA1, BRCA2, hereditary breast and ovarian cancer, pathogenic variants, next-generation sequencing, Dominican Republic, Caribbean

Posted Date: July 2nd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10208004/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Human Genomics on October 23rd, 2026. See the published version at https://doi.org/10.1186/s40246-026-01037-3.

Abstract

Background

Despite the rapid expansion of hereditary cancer testing worldwide, Caribbean populations remain underrepresented in BRCA reference datasets, limiting accurate variant interpretation and equitable implementation of precision medicine. This study expands genomic representation in the Caribbean by characterizing the germline BRCA1/BRCA2 variant spectrum in the first national cohort from the Dominican Republic.

Methods

We retrospectively analyzed 648 consecutively referred individuals using next-generation sequencing. Variants were classified according to ACMG/AMP recommendations and findings were contextualized with published Caribbean, Latin American, and African-ancestry data.

Results

Twenty-seven individuals (4.2%) carried pathogenic or likely pathogenic BRCA variants representing 15 distinct variants. BRCA2 variants predominated. Comparison with published datasets showed partial overlap with neighboring populations while highlighting a distinctive Caribbean variant spectrum. Recurrent variants were identified; however, the available data are insufficient to infer a founder effect.

Conclusions

This study expands BRCA1/BRCA2 genomic diversity data from the Caribbean by providing the first national reference dataset from the Dominican Republic. The findings support improved variant interpretation, genetic counseling, and precision medicine while contributing to better genomic representation of Caribbean populations.

1. INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy among women worldwide, and ovarian cancer continues to carry the highest case-fatality ratio among gynecologic cancers; together, they accounted for an estimated 2.3 million and 324,000 new diagnoses, respectively, in the most recent global cancer statistics report [1]. Hereditary breast and ovarian cancer (HBOC) syndrome, caused predominantly by germline pathogenic variants in *BRCA1* and *BRCA2*, account for approximately 25–30% of familial breast cancer and a substantial share of ovarian cancer occurring outside a sporadic context [2]. Since their identification in the mid-1990s, *BRCA1* and *BRCA2* have been recognized as the most clinically significant tumor-suppressor genes predisposing to HBOC [2]. Germline pathogenic variants in

these genes substantially increase lifetime cancer risk: *BRCA1* carriers face up to 72% cumulative breast cancer risk and 44% ovarian cancer risk by age 80, while *BRCA2* carriers face up to 69% and 17%, respectively [31]. The encoded proteins coordinate DNA double-strand break repair through homologous recombination, and their loss of function underlies the clinical concept of "BRCAness."

Beyond risk assessment, *BRCA1/2* testing has become a cornerstone of precision oncology. Tumors harboring pathogenic *BRCA1/2* variants show increased sensitivity to platinum-based chemotherapy and the poly (ADP-ribose) polymerase (PARP) inhibitors, which exploit synthetic lethality created by homologous recombination deficiency [4]. Identification of a pathogenic variant, therefore, informs not only of surveillance and risk-reducing strategies for unaffected carriers but also of direct therapeutic selection for patients already diagnosed with cancer.

During the three decades following their discovery, extensive geo-ethnic differences in the frequency and spectrum of *BRCA1/2* variants have been documented, including population-specific founder variants in groups such as Ashkenazi Jews and several North African populations [6]. Despite this progress, public variant databases and clinically validated reference panels remain disproportionately derived from European-ancestry and North American cohorts. A recent systematic review and meta-analysis of 45 studies comprising approximately 44,000 breast cancer patients confirmed substantial, statistically significant ethnic variation in *BRCA1/2* mutation prevalence and spectrum and explicitly called for the inclusion of underrepresented groups to improve the accuracy of global risk assessment [6]. This Eurocentric bias in reference data is even more pronounced for populations of African ancestry: a 2026 scoping review of hereditary ovarian cancer in women of African ancestry identified only 30 eligible studies worldwide, most conducted in the United States or North Africa, and explicitly excluded Caribbean populations from analysis because no qualifying genomic studies could be located for the region, despite their substantial African, European, Asian, and Indigenous American admixture [7]. A parallel systematic review of breast cancer genomics in continental African populations similarly identified only ten qualifying studies from seven countries over a twenty-year period, underscoring how little comparable data exist even on the African continent itself [8]. This scarcity of population-specific data has direct clinical consequences: public databases such as ClinVar aggregate evidence largely contributed by laboratories and research consortia operating in well-resourced, predominantly European-ancestry health systems, and a variant that is rare or absent from these reference sets is, by default, more likely to be classified as a variant of uncertain significance (VUS) regardless of its true biological effect [9, 10]. For admixed and historically understudied populations, this asymmetry in available evidence translates into a disproportionate burden of inconclusive genetic test results and limits the precision of cascade testing and genetic counseling for at-risk relatives.

The Dominican Republic occupies a distinctive position within this global landscape. Its population reflects a tri-hybrid genomic ancestry shaped by Indigenous Taíno, Iberian European, and West/Central African contributions, with the African component predominating in most genomic ancestry estimates of Hispaniola [32]. This ancestral configuration is not adequately represented by any single comparator population in the existing *BRCA1/2* literature: it is neither equivalent to the African American cohorts that

dominate the available African-ancestry data, nor interchangeable with the mestizo populations most often sampled in Mexican, Andean, or Southern Cone Latin American studies [13, 14]. To date, no large-scale characterization of the *BRCA1/2* pathogenic variant spectrum has been reported for the Dominican Republic, or, to our knowledge, for any Afro-Caribbean nation using a Caribbean-based clinical cohort.

In this study, we report the spectrum and frequency of *BRCA1/2* germline pathogenic variants identified through targeted NGS in a clinically referred cohort from the Dominican Republic, the largest such dataset reported for the Caribbean region to date. We hypothesized that, consistent with the population's tri-hybrid ancestry, the Dominican *BRCA1/2* variant spectrum would show partial overlap with variants previously reported in both Latin American and African-ancestry cohorts, while also harboring variants not previously documented in either reference group. We further sought to characterize the burden of co-occurring variants of uncertain significance, to critically evaluate the evidentiary basis for a previously suggested founder effect, and to discuss the implications of these findings for genetic counseling, variant reclassification efforts, and the implementation of precision oncology in the Caribbean.

2. MATERIALS AND METHODS

2.1. Study design and subjects

This retrospective cohort study included 649 individuals who presented to Referencia Laboratorio Clínico (Santo Domingo, Dominican Republic) for clinical *BRCA1/2* testing between 2022 and 2025. The majority presented with a personal history of breast and/or ovarian cancer or a significant family history of HBOC-associated malignancies; both male and female participants were included. Each participant provided written informed consent for inclusion of de-identified results in research databases and publications. Whole blood was collected for genomic DNA extraction, and samples were anonymized before analysis. One sample originating from a non-Dominican resident was excluded to preserve the population specificity of the cohort, yielding a final analytic cohort of 648 individuals, of whom 27 tested positive for a pathogenic *BRCA1/2* variant. The study was approved by the National Bioethics Committee (CONABIOS), Dominican Republic (Ref. 014-2026)

2.2. BRCA-Targeted Next-Generation Sequencing

Two complementary NGS platforms were employed [5]. For the first platform, genomic DNA was isolated from peripheral blood leukocytes using the Maxwell® RSC Blood DNA Kit (Promega). Library preparation was performed using the AmpliSeq™ BRCA Panel (Illumina, San Diego, CA, USA), ensuring high-depth coverage of all *BRCA1* and *BRCA2* coding exons and intron-exon boundaries per the manufacturer's instructions. Pooled libraries were sequenced on a MiSeq sequencer (Illumina) using the MiSeq Reagent Kit v2. Raw sequencing data quality was evaluated using Illumina's BaseSpace, and final variant calling was performed with SOPHiA DDM™ for Genomics. For the second platform, the Genexus™ Integrated Sequencer (Thermo Fisher Scientific) was used with the Oncomine™ BRCA Assay GX, and genomic data were analyzed using Genexus™ Software v6.8. (Fig. 1).

2.3. Variant curation and classification

All identified variants were standardized according to Human Genome Variation Society (HGVS) nomenclature guidelines using reference sequences NM_007294.4 (*BRCA1*) and NM_000059.4 (*BRCA2*). Each variant was cross-referenced for genomic location and annotated at both coding DNA and protein levels. Clinical classification was assigned according to ClinVar database entries current at the time of analysis, interpreted in the framework of the ACMG/AMP sequence variant interpretation guidelines [9]. Manual curation reconciled discrepancies in variant notation between the two sequencing platforms and ensured accurate gene- and sample-level assignment, producing a unified, coherent database suitable for statistical analysis.

2.4. Comparative literature search

To contextualize Dominican findings against other populations, we performed a structured, non-systematic literature search for *BRCA1/2* cohort studies from Latin American countries (Mexico, Brazil, Colombia, Peru, Argentina, and Chile) and from populations of African ancestry, prioritizing studies published between 2021 and 2026 and supplementing with earlier landmark reports where regional data were otherwise unavailable. Each of the 15 pathogenic variants identified in the Dominican cohort was individually cross-referenced against a curated comparator dataset of *BRCA1/2* variants previously reported in individuals of African ancestry or origin, which records, for each variant, the number of independent reports in self-reported African-ancestry (SRAA) individuals and a categorical determination of the likelihood that the variant is of African origin (1, likely African, ≥ 75%; 2, possibly African, 50–99%; 3, probably not African, 25–49%; 4, unlikely African, < 25%) [15]. No new statistical comparisons across cohorts were calculated beyond those already reported in the source publications; where exact quantitative comparison was not possible because of differing denominators or reporting conventions, concordance is discussed qualitatively.

2.5. Statistical Analysis

Descriptive statistics (frequencies and percentages) were used to characterize the cohort and variant spectrum. Given the small number of pathogenic carriers, point estimates for subgroup frequencies (e.g., variant-specific carrier proportions) should be interpreted as descriptive rather than precise population estimates.

3. RESULTS

3.1. Cohort characteristics

A total of 649 individuals from the Dominican Republic underwent targeted *BRCA1/2* NGS analysis between 2022 and 2025. One sample, originating from a non-Dominican resident, was excluded to preserve the population specificity of the dataset, yielding a final analytic cohort of 648 individuals. Pathogenic variants were identified in 27 individuals, corresponding to a positivity rate of 4.2% (95% CI,

2.9-6.0%) in this clinically referred cohort. All 27 carriers were heterozygotes and confirmed Dominican residents. Among the 27 carriers, two pairs of biological siblings and one mother-son pair were identified, consistent with family-based referral patterns and with vertical transmission of the identified variants within these families (Table 1).

Table 1
Characteristics of the Dominican cohort

Characteristic	Value
Study period	2022–2025
Referral basis	Personal and/or family history of breast and/or ovarian cancer
Total individuals tested	649
Excluded (non-Dominican resident)	1
Final analytic cohort	648
Pathogenic BRCA1/2 carriers, n (%)	27 (4.2%); 95% CI 2.9-6.0%
BRCA1 carriers, n (% of carriers)	11 (40.7%)
BRCA2 carriers, n (% of carriers)	16 (59.3%)
Distinct pathogenic variants identified	15 (8 BRCA1; 7 BRCA2)
Carrier zygosity	Heterozygous in all 27 carriers
Family clusters identified among carriers	3 (2 sibling pairs; 1 mother-son pair)
Carriers with a concurrent VUS, n (%)	5/27 (18.5%); 4 independent findings
VUS as sole finding, full cohort, n (%)	55/648 (8.5%); 95% CI 6.6–10.9%
Carriers residing in Santo Domingo province, n (%)	14/27 (51.9%)

Abbreviations: CI, confidence interval; VUS, variant of uncertain significance.

3.2. Frequency and spectrum of pathogenic variants

Fifteen distinct pathogenic variants were identified among the 27 carriers: 8 in *BRCA1*, accounting for 11 of the 27 carriers (40.7%), and 7 in *BRCA2*, accounting for 16 of the 27 carriers (59.3%) (Table 2, Table 3). Among the 15 pathogenic variants, 7 were frameshift (indels), 1 was a frameshift (insertion), 5 were stop-gain (nonsense) variants, 1 was a missense substitution, and 1 was a canonical splice-site variant. All 15 variants were classified as pathogenic in ClinVar at the time of analysis (Fig. 2).

Table 2
Pathogenic BRCA1 variants identified in the Dominican cohort

DNA change	Protein change	Exon	Variant type	Carriers, n	Previously reported elsewhere*
c.514del	p.Gln172AsnfsTer62	7	Frameshift deletion	1	—
c.815_824dup	p.Thr276AlafsTer14	10	Frameshift duplication	2	Senegal, Bahamas, Côte d'Ivoire, France, USA, Spain [15]
c.2800C > T	p.Gln934Ter	10	Stop-gain (nonsense)	1	—
c.4065_4068del	p.Asn1355fs	10	Frameshift deletion	1	Nigeria, Sudan [15]; recurrent variants also catalogued in Latin American cohorts [11]
c.4222C > T	p.Gln1408Ter	11	Stop-gain (nonsense)	1	—
c.4327C > T	p.Arg1443Ter	12	Stop-gain (nonsense)	3	Mexico [13]; Trinidad, France, USA [15]; recurrent variants catalogued in Argentine series [19]
c.4484G > T	p.Arg1495Met	13	Missense	1	USA [15]
c.5431C > T	p.Gln1811Ter	22	Stop-gain (nonsense)	1	—

Reference sequence NM_007294.4. Cross-referencing against the curated African-ancestry comparator dataset [15] and regional Latin American literature [11, 13, 19] as cited; a dash (—) indicates the variant was not identified in either source at the time of this analysis and should not be interpreted as evidence that the variant is absent from other populations.

Table 3
Pathogenic BRCA2 variants identified in the Dominican cohort

DNA change	Protein change	Exon	Variant type	Carriers, n	Previously reported elsewhere*
c.1796_1800del	p.Ser599Ter	10	Frameshift deletion	2	Nigeria, USA [15]
c.2808_2811del	p.Ala938Profs	11	Frameshift deletion	1	Nigeria, Brazil, USA [15]; reported across multiple South American countries [14]
c.2830A > T	p.Lys944Ter	11	Stop-gain (nonsense)	1	—
c.5049_5050insT	p.Thr1684TyrfsTer5	11	Frameshift insertion	1	—
c.6486_6489del	p.Lys2162fs	11	Frameshift deletion	7	Europe, North America, Australia, Asia [15]; previously identified in Latin American and African-ancestry populations [3, 13, 16]
c.6487C > T	p.Gln2163Ter	11	Stop-gain (nonsense)	2	—
c.8755-1G > A	p.?	22	Splicing variant	2	—

Reference sequence NM_000059.4. Cross-referencing against the curated African-ancestry comparator dataset [15] and regional Latin American literature [3, 13, 14, 16] as cited; a dash (—) indicates the variant was not identified in either source at the time of this analysis and should not be interpreted as evidence that the variant is absent from other populations.

3.3. Distribution across functional domains

Four of the eight *BRCA1* pathogenic variants (50%) were in exon 10, which overlaps the ovarian cancer cluster region (OCCR); pathogenic variants within this domain have been associated with relatively greater ovarian cancer risk compared with variants outside this domain [3]. Five of the seven *BRCA2* pathogenic variants (71%) were in exon 11, which encodes the eight BRC repeats mediating the interaction between BRCA2 and RAD51, the central recombinase of homologous recombination. Disruption of this interaction is expected to impair double-strand break repair and contribute to increased cancer risk [3]. This clustering in functionally critical regions is consistent with established genotype-phenotype correlations and underscores the biological relevance of exon location to penetrance among HBOC mutation carriers in this cohort.

3.4. Recurrent variants

The variant *BRCA2* c.6486_6489del p.(Lys2162fs) was the most frequently detected in the cohort, identified in 7 of 27 carriers (25.9%; 95% CI, 13.2–44.7%, reflecting the small number of total carriers). This 4-base-pair deletion in exon 11 produces a frameshift beginning at amino acid position 2162, generating a prematurely truncated protein. Its disproportionate representation relative to the remaining 14 pathogenic variants is noteworthy; the genetic and historical basis for this recurrence, including the evidence required to distinguish a population founder effect from chance enrichment in a referral-based cohort, is addressed in the Discussion (Section 4.1). *BRCA2* c.6486_6489del has previously been reported in European, Latin American, and African-ancestry populations, indicating broad geographic distribution rather than a single, geographically restricted origin (Table 4) [3, 13, 16].

Table 4
Comparison of BRCA findings across Latin American and African-ancestry cohorts

Population / Country	Study	Cohort size	Pathogenic BRCA1/2 yield	Notes
Dominican Republic	This study	648 referred individuals	4.2% (27/648)	BRCA2 carriers (n = 16) outnumbered BRCA1 carriers (n = 11); no variant meets the evidentiary threshold for a confirmed founder mutation
Mexico	Fernández-Lopez et al., 2019 [13]	3,985 population samples + 66 breast cancer patients	0.376% (population); 18% (breast cancer patients)	Population-based and clinical cohort yields differ substantially; BRCA1 c.4327C > T is shared with the Dominican cohort
Argentina	Solano et al., 2021 [19]	2,155 breast/ovarian cancer patients	Reported among the higher end of regional referral-based yields	Large population-based multigene panel cohort; recurrent BRCA1/2 variants catalogued
Brazil	Duarte et al., 2024 [16]	12 patients (pilot cohort)	2/12 pathogenic + 1 novel candidate pathogenic variant	Small pilot NGS panel cohort from southern Brazil
Colombia (general)	Rodríguez Rojas et al., 2025 [20]	307 breast cancer patients	19% pathogenic/likely pathogenic overall (BRCA1 17%, BRCA2 14% of positives)	111-gene panel; ATM proposed as a possible additional susceptibility gene (“BRCA3”)
Colombia (African descent)	Vargas et al., 2022 [24]	60 Afro-Colombian families	3.9–33.3%, depending on breast-only vs. breast-and-ovarian subgroup	Haplotype analysis confirmed a shared founder variant between Afro-Colombian and White/mestizo Colombian carriers
Peru	Ferreyra et al., 2023 [22]	525 patients (143 breast, 382 ovarian cancer)	Higher yield among ovarian cancer patients than breast cancer patients	Cohort enriched for PARP-inhibitor treatment candidacy
Chile	Martin et al., 2024 [18]	722 breast/ovarian cancer patients	14% pathogenic/likely pathogenic	31% of results included a VUS; 7 previously unreported BRCA1 variants identified

Given substantial heterogeneity in referral criteria, panel composition, and reporting conventions across these studies, this table presents qualitative concordance rather than a pooled statistical estimate. SRAA, self-reported African ancestry.

Population / Country	Study	Cohort size	Pathogenic BRCA1/2 yield	Notes
African ancestry (pooled, SRAA)	Friebel et al., 2019 [15]	Multi-study curated comparator dataset	Variant-level documentation, not a single cohort prevalence	8 of 15 Dominican pathogenic variants documented; only BRCA1 c.815_824dup meets criteria for “possibly African” origin
Given substantial heterogeneity in referral criteria, panel composition, and reporting conventions across these studies, this table presents qualitative concordance rather than a pooled statistical estimate. SRAA, self-reported African ancestry.				

Table 5

A. Variants of uncertain significance co-occurring with a pathogenic variant

Gene	VUS (DNA / protein change)	Co-occurring pathogenic variant	Individuals, n
BRCA1	c.5348T > C, p.(Met1783Thr)	BRCA1 c.2800C > T	1
BRCA2	c.5498A > G, p.(Asn1833Ser)	BRCA2 c.5049_5050insT	1
BRCA2	c.6412G > T, p.(Val2138Phe)	BRCA1 c.4222C > T	1
BRCA2	c.6412G > T, p.(Val2138Phe)	BRCA2 c.1796_1800del	2 (1 family)
Total: 5 individuals; 4 independent genetic findings (one BRCA2 c.1796_1800del / c.6412G > T combination was co-inherited within a single family and is counted once at the family level).			

3.5. Geographic distribution within the Dominican Republic

The province of residence was available for 25 of the 27 pathogenic carriers. The greatest carrier frequency was observed in Santo Domingo, the nation's capital and most populous metropolitan area, which accounted for 14 of 27 carriers (51.9%), consistent with its proportionally larger contribution to the clinical referral base. The remaining carriers were distributed across Santiago, La Romana, Sosúa, Yaguate, Haina, Azua, Nizao, Higüey, Punta Cana, La Vega, and one additional western province, with no more than one carrier identified per locality outside Santo Domingo. This pattern is consistent with diffuse distribution across the country rather than a defined spatial clustering pattern (Fig. 3).

3.6. Variants of Uncertain Significance

Variants of uncertain significance (VUS) were common in this cohort. A concurrent VUS was identified in 5 of the 27 pathogenic carriers (18.5%), corresponding to 4 independent genetic findings: in one instance, a sibling/parent-child pair (Section 3.1) co-inherited an identical pathogenic variant (*BRCA2* c.1796_1800del) together with the same VUS (*BRCA2* c.6412G > T), consistent with linked transmission within that family rather than two independent events (Table 5A). Considering the entire 648-person cohort, an additional 55 individuals (8.5%; 95% CI, 6.6–10.9%) carried a VUS as their sole *BRCA1/2*

finding, in the absence of a concurrent pathogenic variant (Table 5B). VUS were identified more often in *BRCA2* (44/55, 80%) than in *BRCA1* (11/55, 20%), and the great majority (43/55, 78%) were missense substitutions.

The most frequently detected VUS in the cohort was *BRCA2* c.6412G > T p.(Val2138Phe), observed in 9 individuals, followed by *BRCA2* c.9976A > T p.(Lys3326Ter), observed in 6 individuals. The latter corresponds to the well-characterized K3326X variant, a truncating change located after the final BRC repeat, in the C-terminal third of the BRCA2 protein; despite predicting premature termination, this variant has been consistently associated with only modest, context-dependent cancer risk in the published literature (odds ratios in the range of approximately 1.2–2.5 across gynecologic, pancreatic, and selected environmentally-associated cancers) and is therefore generally classified as a VUS or low-penetrance allele rather than a fully pathogenic truncating variant [17]. Its detection in 6 of 648 Dominican individuals (0.9%) is consistent with its recognized status as a relatively common, recurrent BRCA2 polymorphism-like variant across diverse populations rather than a Dominican-specific finding.

3.7. Comparison with Latin American and African-Ancestry Cohorts

To contextualize the Dominican *BRCA1/2* spectrum, we compared our findings with published cohorts from five additional Latin American countries (Mexico, Brazil, Colombia, Peru, and Argentina) and with the published literature on populations of African ancestry (Fig. 4).

Overall positivity and gene distribution. The 4.2% pathogenic variant yield observed in this clinically referred Dominican cohort falls within the range reported across Latin American referral-based cohorts, which spans from approximately 1.2% in unselected breast cancer series to double digits in cohorts enriched for early-onset or strong family history; a 2016 review of 33 studies across 13 Central and South American countries reported prevalence estimates spanning 1.2–47.8% depending on selection criteria, narrowing to 1.2–4.9% within unselected breast cancer cohorts specifically [14, 18]. Individual recent cohorts illustrate this same heterogeneity: a population-based Argentine series of 2,155 breast/ovarian cancer patients identified pathogenic *BRCA1/2* variants in a comparable range to ours [19]; a Colombian multigene panel study of 307 patients from the southwest of the country reported pathogenic or likely pathogenic *BRCA1* and *BRCA2* variants in 17% and 14% of carriers, respectively, considerably higher than our cohort, reflecting differences in referral criteria and panel composition [20]; a systematic review and data-mining synthesis of *BRCA1/2* pathogenic variants reported in the Mexican population corroborates this pattern of substantial inter-study variability even within a single country [21]; a Peruvian series of 525 breast and ovarian cancer patients similarly reported a higher combined yield, consistent with its enrollment of patients already diagnosed with ovarian cancer, a subgroup with a substantially higher *BRCA1/2* positivity rate than unselected breast cancer referrals [22]; and a Chilean multigene panel cohort of 722 patients reported a 14% pathogenic/likely-pathogenic *BRCA1/2* yield, within the broader Latin American range [18]. As in our cohort, *BRCA2* pathogenic variants outnumbered *BRCA1* variants in several of these series, including the Chilean and Colombian cohorts [18, 20].

Shared and overlapping variants. Direct variant-level overlap with other Latin American cohorts was limited but present. *BRCA1* c.4327C > T (p.Arg1443Ter), detected in 3 of our 27 carriers, has been independently reported in a Mexican hereditary breast cancer cohort (FUCAM registry) [13] and has also been documented in Trinidadian and French cohorts in the African-ancestry comparator dataset described below [15]. *BRCA2* c.2808_2811del has been reported across multiple South American countries, including Argentina, Brazil, Colombia, Peru, and Venezuela, as well as in Nigerian and Brazilian individuals of African ancestry [15]. None of the remaining 13 Dominican pathogenic variants corresponded to the high-frequency, population-defining variants reported in the largest available Hispanic/Latino forest-plot analyses to date, such as *BRCA1* c.2612C > T or *BRCA2* c.4563A > G, which were identified as the most prevalent alleles in a 2026 meta-analysis pooling Hispanic/Latino cohorts from across the Americas [6]. This absence of overlap with previously described high-frequency Latino alleles suggests that the Dominican *BRCA1/2* spectrum, while sharing individual variants with neighboring countries, is not a simple subset of the variant profile most reported for "Hispanic/Latino" cohorts in the literature, a category that has historically underrepresented Caribbean and Afro-Latino populations specifically.

Comparison with African-ancestry cohorts. Cross-referencing our 15 pathogenic variants against a curated dataset of *BRCA1/2* variants previously reported in self-reported African-ancestry (SRAA) individuals identified 8 of 15 Dominican variants (53%) with at least one prior report in an SRAA cohort: *BRCA1* c.815_824dup, c.4065_4068del, c.4327C > T, and c.4484G > T; and *BRCA2* c.1796_1800del, c.2808_2811del, c.2830A > T, and c.6486_6489del [15]. This proportion is consistent with the substantial West/Central African ancestral contribution to the Dominican gene pool and with the original report describing this cohort. However, a more granular evaluation of the same comparator dataset, which additionally estimates the probability that each variant is specifically of African origin (rather than merely having been observed in at least one African-ancestry individual), showed that only one of these eight variants, *BRCA1* c.815_824dup, met criteria for "possibly African" origin (50–99% probability); the remaining seven, including the recurrent *BRCA2* c.6486_6489del, were classified as "unlikely African" (< 25% probability), reflecting their broad documentation across North American, European, Asian, and Australian cohorts in addition to African-ancestry individuals [15]. This distinction is clinically important: documentation of a variant in an African-ancestry individual is not equivalent to evidence that the variant specifically arose within, or is enriched in, African-ancestry lineages. *BRCA1* c.815_824dup, the variant with the strongest African-origin signal in this analysis, has been independently reported in Senegal, the Bahamas, Côte d'Ivoire, and other African-diaspora populations [15], and its detection in 2 of our 27 Dominican carriers (7.4%) is compatible with, though not proof of, transmission along the same West African ancestral lineage proposed for these other reports.

Taken together, these comparisons indicate that the Dominican *BRCA1/2* variant spectrum is best understood not as a discrete national profile but as a mosaic reflecting the population's documented tri-hybrid ancestry, with partial, variant-specific overlap with both Latin American and African-ancestry reference datasets and no single dominant "Dominican founder" variant identified with the level of evidence required to support that designation (Section 4.1).

4. DISCUSSION

4.1. Principal's findings

This study provides the first large-scale genomic characterization of *BRCA1/2* germline pathogenic variants in the Dominican Republic, filling a long-standing gap in the genetic epidemiology of HBOC in the Caribbean. A pathogenic variant yield of 4.2% in a clinically referred cohort is broadly consistent with frequencies reported in Latin American referral-based studies more generally, and the 15-variant spectrum identified spans both truncating and missense mechanisms clustered in functionally established domains of both genes.

The most frequent variant in this cohort, *BRCA2* c.6486_6489del, was identified in 7 of 27 carriers. Recurrent detection of a single variant within a referral-based cohort is sometimes interpreted as presumptive evidence of a population founder effect; we deliberately avoid this conclusion here. Establishing a founder mutation requires more than recurrence within one cohort: rigorous designation typically rests on haplotype analysis demonstrating that carriers share a common ancestral chromosomal segment surrounding the variant, ideally combined with a coalescent or genealogical estimate of when the variant arose, and confirmation that the variant is geographically or ethnically restricted rather than broadly distributed [23]. Population-genetic analyses of haplotype-dated *BRCA1/2* founder variants in other populations have shown that confirmed founder alleles typically arose within the last few thousand years and are largely confined to a single or a small number of ethnic groups [23]. By these criteria, the evidence available for *BRCA2* c.6486_6489del falls short: no haplotype data were generated in this study, and the variant has independently been reported in European, Latin American, and African-ancestry populations, indicating a broad geographic distribution incompatible with a narrowly restricted founder origin (Table 4) [3, 13, 16]. We therefore describe the recurrent detection of this variant as evidence that it may be enriched within the Dominican clinical referral population studied here; however, dedicated haplotype and ancestry-informative marker studies, ideally extended to apparently unrelated carrier families, are required before a founder effect specific to the Dominican Republic can be inferred. A useful comparator is provided by a haplotype-confirmed founder mutation recently described in Afro-Colombian and White/mestizo Colombian patients sharing *BRCA2* c.2701delC, where haplotype analysis of carriers from both ancestry groups demonstrated a shared ancestral origin [24]; no equivalent analysis has yet been performed for any Dominican *BRCA1/2* variant, and this represents a clear and actionable next step rather than a limitation that diminishes the value of the present dataset.

4.2. Comparison with Latin American populations

The Dominican *BRCA1/2* spectrum shares individual variants with cohorts from Mexico, Argentina, Brazil, Colombia, and Peru, but does not closely mirror the high-frequency variants most often reported in pooled Hispanic/Latino analyses, several of which derive disproportionately from Mexican-American and mestizo cohorts in the continental United States and Mexico [6, 13]. This partial divergence is consistent with the historical and demographic distinctiveness of the Dominican Republic relative to the Spanish-

colonial mestizo populations that dominate much of the existing Latin American *BRCA1/2* literature: while both groups share a Spanish colonial history, the proportion and source of African ancestry, the near-absence of a large surviving Indigenous genetic contribution outside the Taíno legacy, and the distinct migratory history of the Caribbean basin collectively produce a genomic background that cannot be assumed to be interchangeable with that of Mexican, Andean, or Southern Cone populations [11, 12, 14]. Regional reviews of Latin American *BRCA1/2* data have long emphasized that the relative proportion of European, Indigenous, and African ancestral components varies substantially across the region, and that founder and recurrent mutation profiles described for one country should not be extrapolated to others without direct confirmation [14]. Our findings reinforce this principle and extend it specifically to the Caribbean, a subregion that has been largely absent from prior Latin American *BRCA1/2* comparative literature.

4.3. Comparison with African-Ancestry Populations

Eight of the 15 Dominican pathogenic variants have previously been reported in individuals of African ancestry, a finding broadly consistent with the substantial West/Central African ancestral contribution documented for the Dominican population [32]. However, as detailed in Section 3.7, a more granular analysis indicates that most of these eight variants are also broadly distributed across non-African-ancestry populations and carry a low computed probability of being specifically of African origin, except for *BRCA1* c.815_824dup [15]. This distinction matters clinically and scientifically: it would be an overstatement to characterize the Dominican *BRCA1/2* spectrum as predominantly "African" in molecular origin based on co-occurrence with African ancestry reports alone. At the same time, the comparison underscores a complementary point repeatedly emphasized in the African-ancestry HBOC literature: the available reference data for populations of African descent remain so limited that even partial overlap is informative. A 2026 scoping review identified only 30 eligible studies of hereditary ovarian cancer in women of African ancestry worldwide; the majority were conducted in the United States or North Africa and explicitly noted the complete absence of qualifying Caribbean data [7]. A parallel systematic review of breast cancer genomics across the African continent itself identified only ten studies from seven countries over two decades [8]. Within this context, the Dominican Republic represents an Afro-Caribbean population that is genomically informative, neither reducible to existing African-ancestry reference cohorts (which are themselves predominantly African American or North African) nor to existing Latin American reference cohorts (which are predominantly mestizo). Generating and publishing this dataset therefore contributes a population genomic node not previously available to either literature and helps close, in a small but concrete way, the broader gap in genomic equity that affects African-descent and Caribbean populations worldwide [6, 7, 8].

4.4. Clinical implications

Knowledge of a patient's *BRCA1/2* mutation status carries direct implications for both cancer risk management and treatment selection, consistent with current consensus clinical management frameworks for hereditary breast and ovarian cancer [25, 26]. For unaffected carriers, identification of a pathogenic variant supports enhanced surveillance, consideration of risk-reducing surgery, and cascade

testing of at-risk relatives. For patients already diagnosed with breast or ovarian cancer, *BRCA1/2* pathogenic variants identify tumors with an increased likelihood of response to platinum-based chemotherapy and to PARP inhibitors, which exploit the synthetic lethality created by homologous recombination deficiency (Section 4.6) [4]. The population-specific variant catalog generated here, including documentation of which variants recur within this clinical referral base, is intended to support more confident and efficient variant interpretation for future Dominican patients tested for the same genes, reducing the proportion of results that remain provisionally uncertain pending additional population data.

4.5. Implications for genetic counseling

VUS present a recurring challenge in clinical genetics, as their pathogenicity cannot be established with currently available evidence. In this cohort, a concurrent VUS was identified in 5 of the 27 pathogenic carriers (18.5%, representing 4 independent genetic findings once a co-inheriting family pair is counted once; Section 3.6), and an additional 55 individuals across the full cohort carried a VUS as their sole finding (8.5%). The co-occurrence of a VUS with an established pathogenic variant does not alter clinical management based on the pathogenic finding, but the VUS itself should not independently influence risk-reduction decisions until it is reclassified based on additional evidence. The detection of *BRCA2* c.9976A > T (K3326X) in 6 individuals in this cohort illustrates this principle well: despite being a truncating, stop-gain variant, its well-documented status in the international literature as a low-penetrance or risk-modifying allele rather than a fully penetrant pathogenic variant means that its presence should be communicated to patients and clinicians as conferring, at most, a modest and incompletely characterized risk modification, not as equivalent to the unambiguously pathogenic frameshift and nonsense variants reported in Table 2 and Table 3 [17]. More broadly, systematic reporting and international data sharing of VUS identified in underrepresented populations is the principal mechanism by which such variants are eventually upgraded to pathogenic, downgraded to benign, or further refined to intermediate-risk categories as population frequency and case-level evidence accumulate [9, 10]. Clinicians providing genetic counseling to Dominican patients should communicate the provisional nature of VUS findings clearly, avoid equating a positive genetic test result with a uniformly high-risk pathogenic finding when the result is in fact a VUS, and ensure that patients are flagged for periodic re-evaluation as variant classifications evolve.

4.6. Precision oncology and PARP inhibitors

The clinical utility of *BRCA1/2* testing extends well beyond risk stratification. Tumors harboring pathogenic *BRCA1/2* variants demonstrate increased sensitivity to platinum-based chemotherapy and to PARP inhibitors, which exploit the synthetic lethality created by homologous recombination deficiency [4]. PARP inhibitors are now established components of treatment for *BRCA*-mutated breast and ovarian cancer across multiple lines of therapy, and rational combination strategies (for example, with DNA damage response or immune-modulating agents) are an active area of clinical investigation aimed at extending benefit and addressing acquired resistance [27]. The ability to stratify patients by germline *BRCA1/2* status is therefore not merely a prognostic tool but a direct enabler of precision oncology, and

accurate population-specific variant interpretation, as generated in this study, is a prerequisite for ensuring that Dominican patients with a true pathogenic variant are correctly identified as candidates for this therapeutic approach rather than left in diagnostic uncertainty because their variant is absent from internationally curated reference databases.

4.7. Population genomics in the Caribbean

The Dominican Republic shares with the rest of the insular Caribbean a documented history of cancer surveillance and research infrastructure that remains less developed than in many higher-income settings: as of the most recent regional assessments, only a minority of the 30 nations and territories that make up the Caribbean basin maintain a population-based cancer registry, and existing registries vary widely in completeness and duration of operation [28, 29]. Regional bodies such as the African-Caribbean Cancer Consortium and the International Agency for Research on Cancer's Caribbean Regional Hub for Cancer Registration have begun to address this gap from a surveillance and epidemiological perspective [28], but comparable coordinated investment in population-specific germline cancer genomics has, to our knowledge, not yet materialized for the Dominican Republic or for most of its Caribbean neighbors. This study, generated through routine clinical testing volume at a single laboratory rather than through a dedicated research consortium, illustrates that clinically accumulated genomic data can nonetheless make a meaningful contribution to addressing this gap, while also highlighting how much additional, coordinated regional investment would be required to generate population-representative (rather than referral-based) prevalence estimates for the Caribbean.

4.8. Limitations

Several limitations merit consideration. First, this is a clinically referred cohort, inherently enriched for HBOC risk through self- or physician-initiated referral based on personal or family cancer history; the 4.2% pathogenic variant yield therefore reflects the diagnostic yield of this referral pathway and cannot be extrapolated to estimate population-level *BRCA1/2* prevalence in the general Dominican population. Second, the absolute number of pathogenic carriers (n = 27) is modest, which widens the confidence intervals around variant-specific frequency estimates (for example, the 95% CI for the proportion of carriers with *BRCA2* c.6486_6489del spans approximately 13% to 45%) and limits the statistical power of any subgroup comparison. Third, ancestry-informative markers and genome-wide ancestry estimates were not generated for this cohort; consequently, statements regarding the population's tri-hybrid ancestry rely on previously published genomic ancestry estimates for the Dominican Republic rather than on direct ancestry data from the tested individuals themselves. Fourth, dedicated haplotype analysis, which would be required to formally evaluate a founder effect for *BRCA2* c.6486_6489del or any other recurrent variant, was beyond the scope of this study and represents the single most important methodological gap to address in follow-up work. Fifth, detailed clinical phenotype data (tumor histology, receptor status, stage at diagnosis, treatment received) and sex distribution were not uniformly available for all participants, limiting genotype-phenotype correlation analyses. Sixth, the comparative analysis in Section 3.7 relied on qualitative cross-referencing against previously published cohorts and a curated African-ancestry variant dataset rather than on harmonized, individual-level meta-analysis, given

substantial heterogeneity in referral criteria, panel composition, and reporting conventions across the source studies.

None of these limitations diminishes the central contribution of this work: the generation of the first systematically curated *BRCA1/2* pathogenic variant dataset for the Dominican Republic, derived from a substantial clinical cohort and curated to a level of detail (exon location, variant type, carrier count, cross-referencing against international comparator datasets) that did not previously exist for this population. Every population-specific *BRCA1/2* dataset reported to date, including the founding reports for now well-established founder mutations in other regions, began as a referral-based clinical series subsequently refined by additional population and haplotype studies; the present dataset is intended to occupy the same role for the Dominican Republic.

4.9. Future directions

Building on the dataset and limitations described above, we propose the following priorities for future work. First, haplotype analysis using single-nucleotide polymorphism markers flanking *BRCA2* c.6486_6489del and other recurrent variants in apparently unrelated Dominican carrier families, to test for a shared ancestral haplotype formally and, if confirmed, to estimate the approximate time since the variant's introduction into the population [23]. Second, expansion from targeted *BRCA1/2* panels toward broader multigene hereditary cancer panels or whole-exome sequencing in Dominican patients who test negative for *BRCA1/2* but retain a strong personal or family cancer history, paralleling recent findings in Colombian and Argentine cohorts that a substantial share of hereditary breast cancer susceptibility in *BRCA1/2*-negative families is attributable to other genes such as *ATM*, *CHEK2*, and *PALB2* [20]. Third, incorporation of ancestry-informative markers or genome-wide genotyping into future Dominican cohorts, to directly quantify individual-level ancestry proportions rather than relying on population-level estimates, and to formally test whether ancestry proportion correlates with carrier status or variant spectrum. Fourth, participation in or formation of a Caribbean-wide hereditary cancer genomics consortium, building on the surveillance and epidemiological infrastructure already established by regional bodies such as the African-Caribbean Cancer Consortium [28, 29], to pool *BRCA1/2* and multigene panel data across Caribbean nations and generate region-representative, rather than single-country, prevalence and spectrum estimates. Fifth, sustained submission of Dominican variant data, particularly VUS such as *BRCA2* c.6412G > T and c.9976A > T, to ClinVar and other international variant curation databases, to accelerate reclassification both for Dominican patients and for the broader international patient population who may share these variants [9, 10, 30]. Sixth, formal population-based (rather than referral-based) screening studies, which would be required to establish a true population-level *BRCA1/2* prevalence estimate for the Dominican Republic, analogous to efforts already underway or proposed in other middle-income settings.

5. CONCLUSIONS

This study provides the first large-scale characterization of *BRCA1/2* pathogenic variants in the Dominican Republic, identifying a spectrum of 15 variants with partial, variant-specific overlap with both

Latin American and African-ancestry reference populations and no single variant meeting the evidentiary threshold for a confirmed founder mutation. These findings provide a population-specific reference for variant interpretation, support more confident genetic counseling and cascade testing for Dominican families, and underscore the continued urgency of expanding genomic databases to include diverse and historically underrepresented populations, including the Afro-Caribbean populations of the Dominican Republic and its regional neighbors, in order to advance equitable implementation of precision oncology globally.

Declarations

ACKNOWLEDGMENTS

The authors thank the patients and families at Referencia Laboratorio Clínico who consented to the use of de-identified genetic data for research purposes, and the laboratory and clinical staff who supported sample collection, sequencing, and variant curation.

AUTHOR CONTRIBUTIONS (CRediT)

Noelia Parra: methodology; investigation; formal analysis; data validation.

Isabel C. Lucero: conceptualization; formal analysis; validation; writing – original draft.

Elizabeth Castell: conceptualization; investigation; data curation; statistical analysis.

Marianna Figueroa: investigation; analysis; visualization.

Thais E. Reyes (Senior Co-Investigator): investigation; formal analysis; writing – original draft; supervision.

Eileen Riego (Principal Investigator / Last Author): conceptualization; supervision; project administration; writing final paper – review & editing.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
2. Sarin R. A decade of discovery of BRCA1 and BRCA2: Are we turning the tide against hereditary breast cancer? J Cancer Res Ther. 2006;2(4):157–8.
3. Rebbeck TR, Mitra N, Wan F, et al. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. JAMA. 2015;313(13):1347–61.
4. Tung NM, Garber JE. BRCA1/2 testing: therapeutic implications for breast cancer management. Br J Cancer. 2018;119(2):141–52.
5. D'Argenio V, Esposito MV, Telese A, et al. The molecular analysis of BRCA1 and BRCA2: Next-generation sequencing supersedes conventional approaches. Clin Chim Acta. 2015;446:221–5.
6. Khan NU, Lei H, Fu J, Lei R, Chen X, Alqarni SS, Chen T. Global prevalence and ethnic variation of pathogenic BRCA1/2 variants in breast cancer: a systematic review and meta-analysis. J Transl Med. 2026;24:555.
7. Rossouw B, Araujo M, Krause A, Baine-Savanhu F. Hereditary ovarian cancer in women with African ancestry: a scoping review. Fam Cancer. 2026;25(1):16.
8. Mugo N, Contino G. Genomic landscapes of breast cancer in African populations: a systematic review. NPJ Breast Cancer. 2025;11.
9. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–24.
10. Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018;46(D1):D1062–7.
11. Jara L, Morales S, de Mayo T, González-Hormazábal P, Carrasco V, Godoy R. Mutations in BRCA1, BRCA2 and other breast and ovarian cancer susceptibility genes in Central and South American populations. Biol Res. 2017;50(1):35.
12. Oluwagbemiga LA, Oluwole A, Kayode AA. Seventeen years after BRCA1: what is the BRCA mutation status of the breast cancer patients in Africa? A systematic review. SpringerPlus. 2012;1:83.
13. Fernández-Lopez JC, Romero-Córdoba S, Rebollar-Vega R, et al. Population and breast cancer patient analyses reveal the diversity of genomic variation in the BRCA genes in the Mexican population. Hum Genomics. 2019;13(1):3.
14. Ossa CA, Torres D. Founder and recurrent mutations in BRCA1 and BRCA2 genes in Latin American countries: state of the art and literature review. Oncologist. 2016;21(7):832–9.
15. Friebel TM, Andrulis IL, Balmaña J, et al. BRCA1 and BRCA2 pathogenic sequence variants in women of African origin or ancestry. Hum Mutat. 2019;40(11):1781–96.
16. Duarte CAB, dos Santos CA, de Oliveira CDD, Spautz CC, Sumita LM, Nakatani SM. Hereditary breast cancer next-generation sequencing panel evaluation in the south region of Brazil: a novel BRCA2

candidate pathogenic variant is reported. Mol Genet Genomic Med. 2024;12(4):e2504.

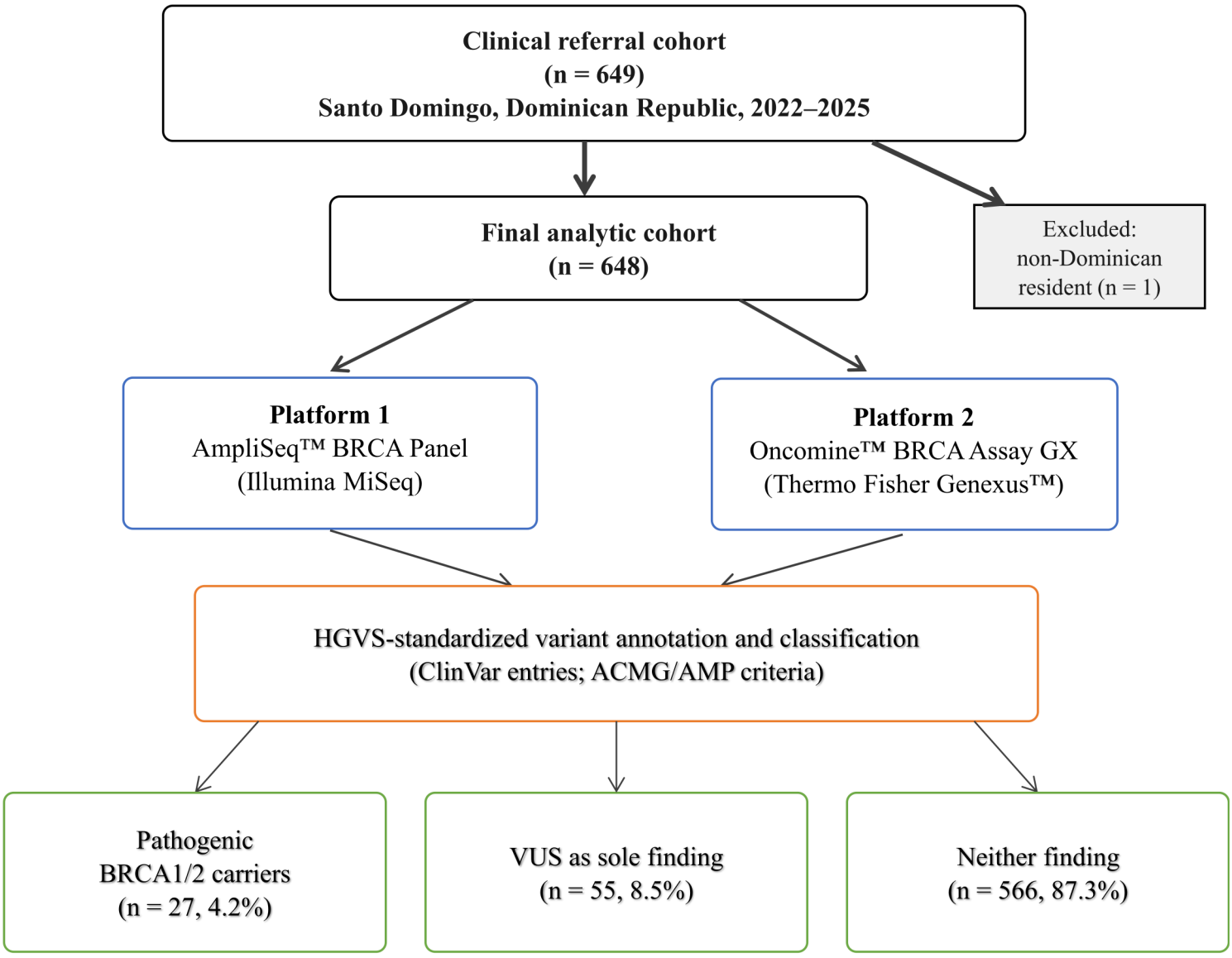
17. Baughan S, Tainsky MA. K3326X and other C-terminal BRCA2 variants implicated in hereditary cancer syndromes: a review. Cancers (Basel). 2021;13(3):447.
18. Martin FJ, Saffie IM, Hurtado MA, Avila-Jaque D, Lagos RA, Selman CA, Huserman JZ, Castillo VA, Chahuán BJ. Variants in BRCA1/2 in a hospital-based cohort in Chile and national literature review. Ecancermedicalscience. 2024;18:1683.
19. Solano AR, Liria NC, Jalil RA, et al. Study of the genetic variants in BRCA1/2 and non-BRCA genes in a population-based cohort of 2155 breast/ovary cancer patients, including 443 triple-negative breast cancer patients, in Argentina. Cancers (Basel). 2021;13(11):2711.
20. Rodríguez Rojas LX, Doza Martínez L, Olave Rodríguez JA, Murillo Rusynke SE, Pérez Castellano PA. Bolaños Beltrán DA, Ortiz Rojas HJ, Nastasi Catanese JA. Germinal mutations among patients with breast cancer in Colombia: is BRCA3 coming? Ecancermedicalscience. 2025;19:1859.
21. Alday-Montañez FD, Dickens-Terrazas D, Mejia-Carmona GE et al. Pathogenic variants in BRCA1 and BRCA2 genes associated with female breast and ovarian cancer in the Mexican population. J Med Life. 2025;18(1).
22. Ferreyra Y, Rosas G, Cock-Rada AM, Araujo J, Bravo L, Doimi F, Casas J, Clavo MÁ, Pinto JA, Belmar-López C. Landscape of germline BRCA1/BRCA2 variants in breast and ovarian cancer in Peru. Front Oncol. 2023;13:1227864.
23. Li J, Zhao B, Huang T, Qin Z, Wang SM. Human BRCA pathogenic variants were originated during recent human history. Life Sci Alliance. 2022;5(6):e202101263.
24. Vargas E, de Deugd R, Villegas VE, Gil F, Mora L, Viaña LF, Bruges R, Gonzalez A, Galvis JC, Hamann U, Torres D. Prevalence of BRCA1 and BRCA2 germline mutations in patients of African descent with early-onset and familial Colombian breast cancer. Oncologist. 2022;27(2):e151–7.
25. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version; 2024.
26. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 2023 Feb 23 [updated 2025]. In: GeneReviews®. Seattle: University of Washington; 1993–2026.
27. Bhamidipati D, Haro-Vinueza A, Sia I, et al. PARP inhibitors: enhancing efficacy through rational combinations. Br J Cancer. 2023;129(6):904–16.
28. Spence D, Argentieri MA, Andall-Brereton G, et al. Advancing cancer care and prevention in the Caribbean: a survey of strategies for the region. Lancet Oncol. 2019;20(9):e522–34.
29. Banydeen R, Rose AMC, Martin D, et al. Advancing cancer control through research and cancer registry collaborations in the Caribbean. Cancer Control. 2015;22(4):520–30.
30. Bose M, Faseela EE, Rossing M, Sørensen CS. Functional assays for BRCA1 and BRCA2 variant analysis: new tools and their applications. NPJ Breast Cancer. 2026. [Article in press].
31. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017;317(23):2402–16.

32. Moreno-Estrada A, Gravel S, Zakharia F, et al. Reconstructing the Population Genetic History of the Caribbean. PLoS Genet. 2013;9(11):e1003925.

Table 5B

Table 5B is available in the Supplementary Files section.

Figures



NGS, Next Generation Sequencing; VUS, Variant of Uncertain Significance. Percentages calculated on the final analytic cohort (n = 648).

Figure 1

Study workflow

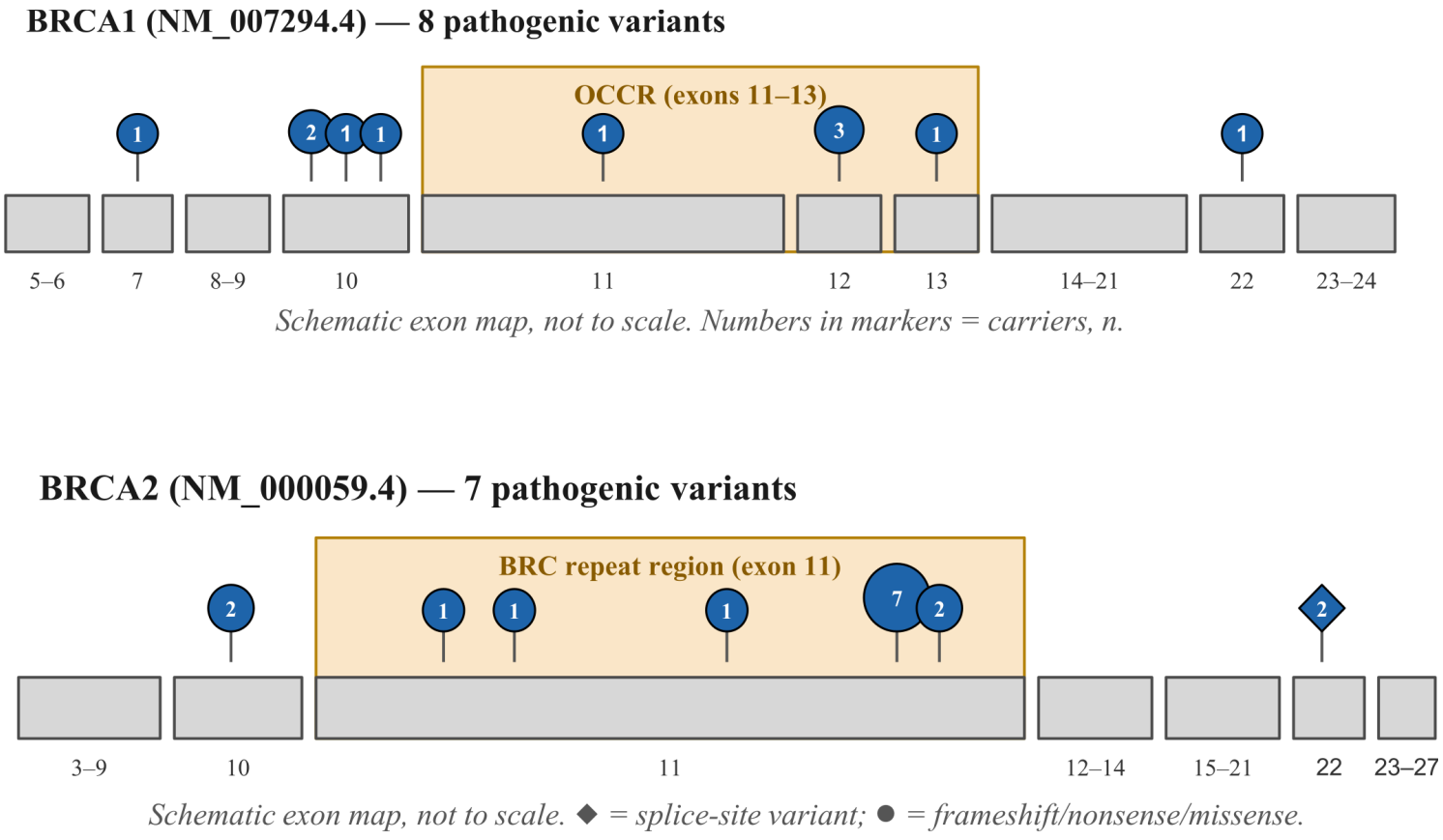
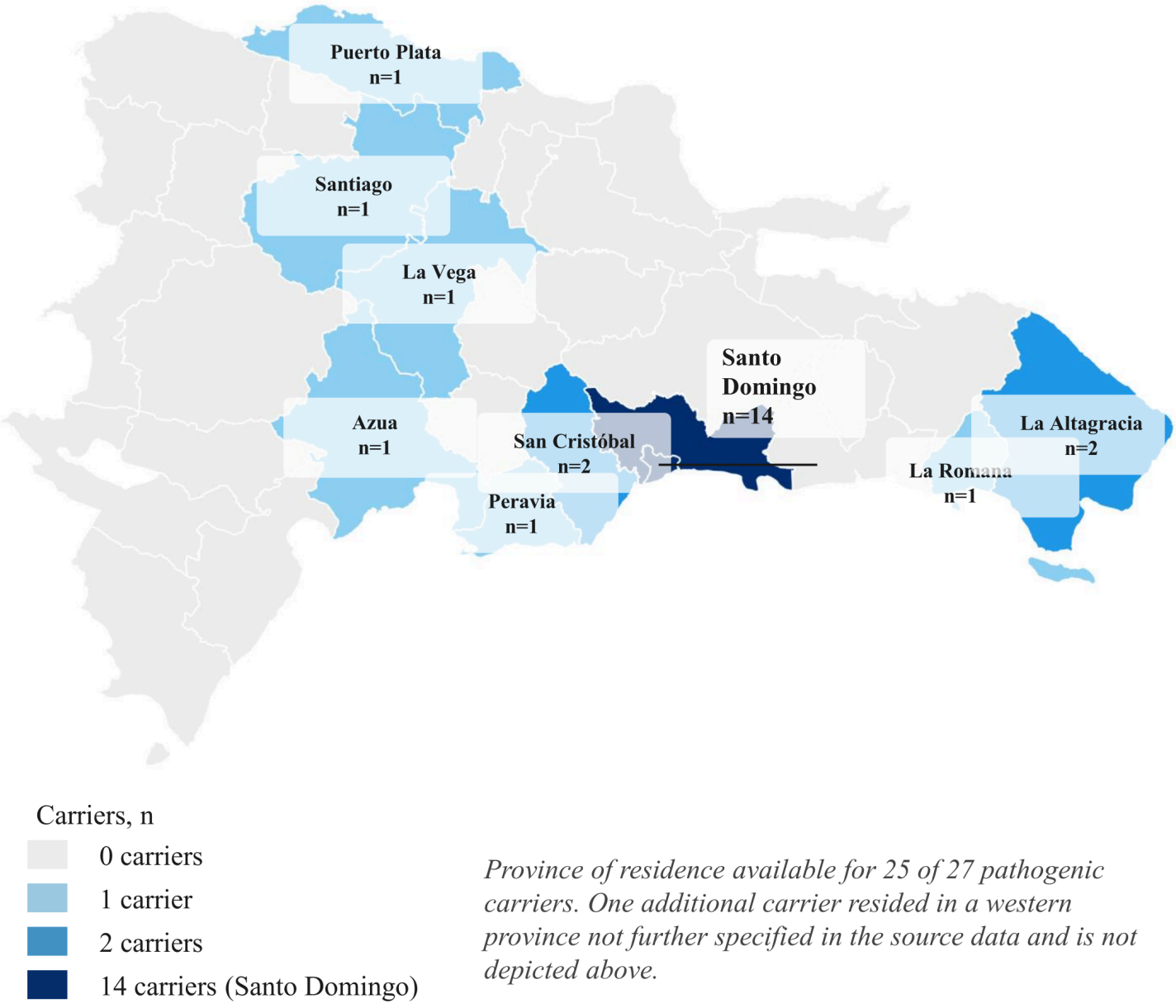


Figure 2

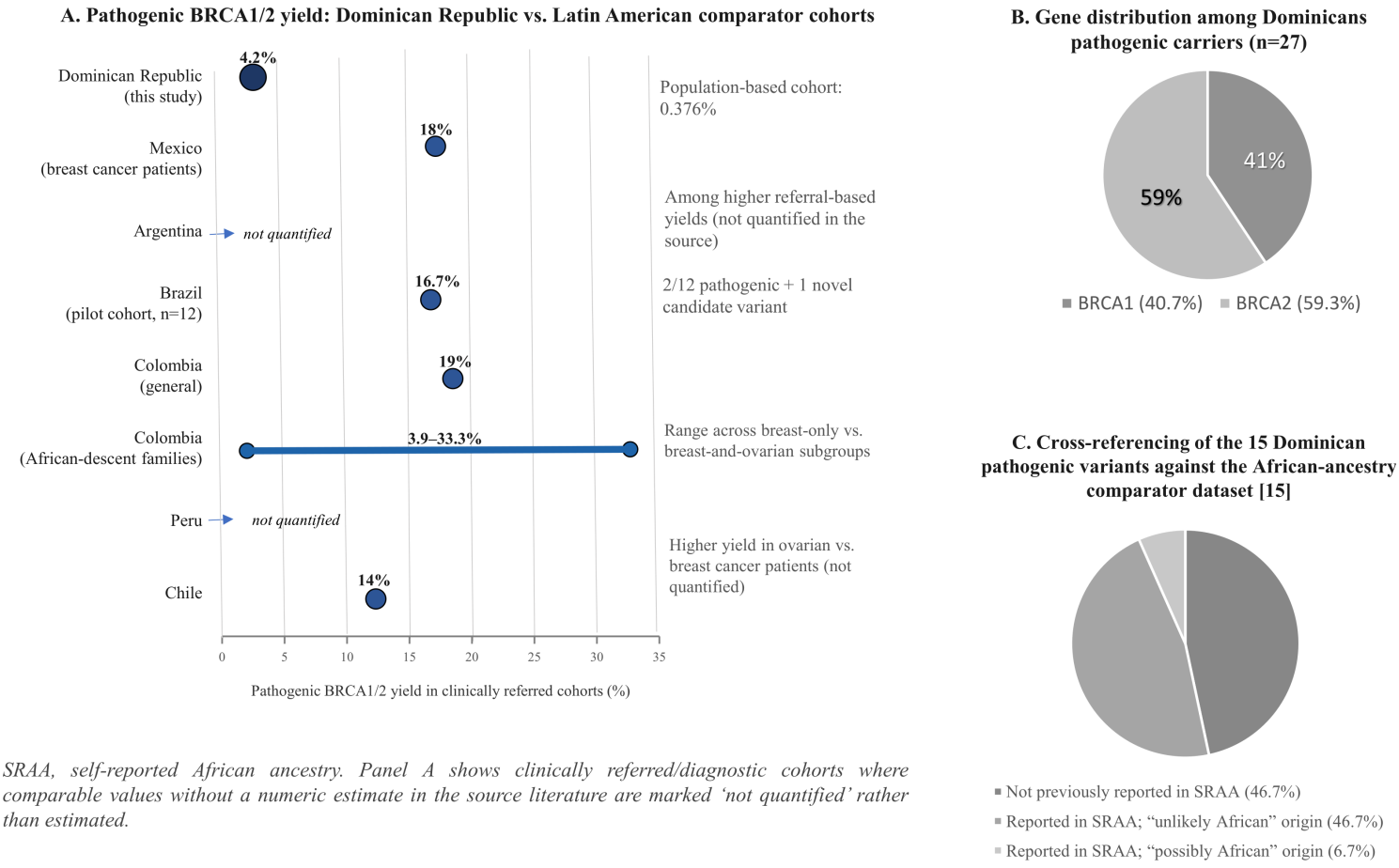
Distribution of BRCA1 and BRCA2 pathogenic variants across functional domains



AI disclosure: Data visualization generated with the assistance of Claude (Claude Sonnet 4.6, Anthropic; anthropic.com). Province boundaries are rendered from a public-domain Dominican Republic administrative GeoJSON as a base map image (not natively editable as vector shapes in PowerPoint, consistent with standard practice for cartographic boundary data); all labels, legend, title, and counts are native, fully editable PowerPoint text/shapes placed directly from carrier counts in Table 1 and Section 3.5 of the manuscript. The author reviewed, verified, and takes full responsibility for the final figure.

Figure 3

Geographic distribution of pathogenic BRCA1/2 variant carriers within the Dominican Republic



SRAA, self-reported African ancestry. Panel A shows clinically referred/diagnostic cohorts where comparable values without a numeric estimate in the source literature are marked ‘not quantified’ rather than estimated.

Figure 4

Comparative pathogenic variant spectrum across Latin American and African-ancestry populations

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryDataBRCADominicanRepublicHumanGenomic.xlsx
- Table5B.docx