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# Genetic Testing in Diverse Populations in South America

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Oncologia D'or

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# Disclosure

- Speaker and teacher for AstraZeneca, MSD, Roche, Bayer, and BMS

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# Topics

- Latin America (LA) – genetic melting-pot
- Genetic counseling in LA
- HBOCS => BRCA1/2 LA
  - BRCA1/2 Brazil
- HBOCS => other genes LA
  - Other genes Brazil
    - TP53 R337H

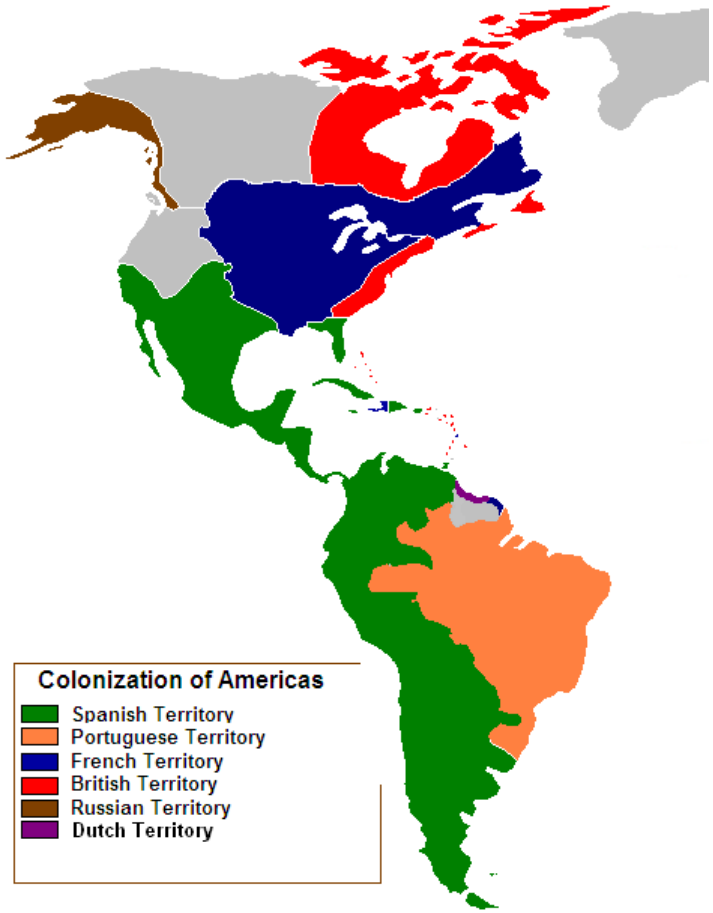
# History of immigration to Latin America

**Americas are characterised by exceptionally high genetic diversity.**

**This has been shaped by historical migrations, such as European Colonialism, the Atlantic Slave Trade and more recent waves of economic migration.**

**These movements of people have resulted in a mosaic of genetic fragments of different ancestry interspersed in present-day American genomes.**

# Colonization of the Americas (1750)

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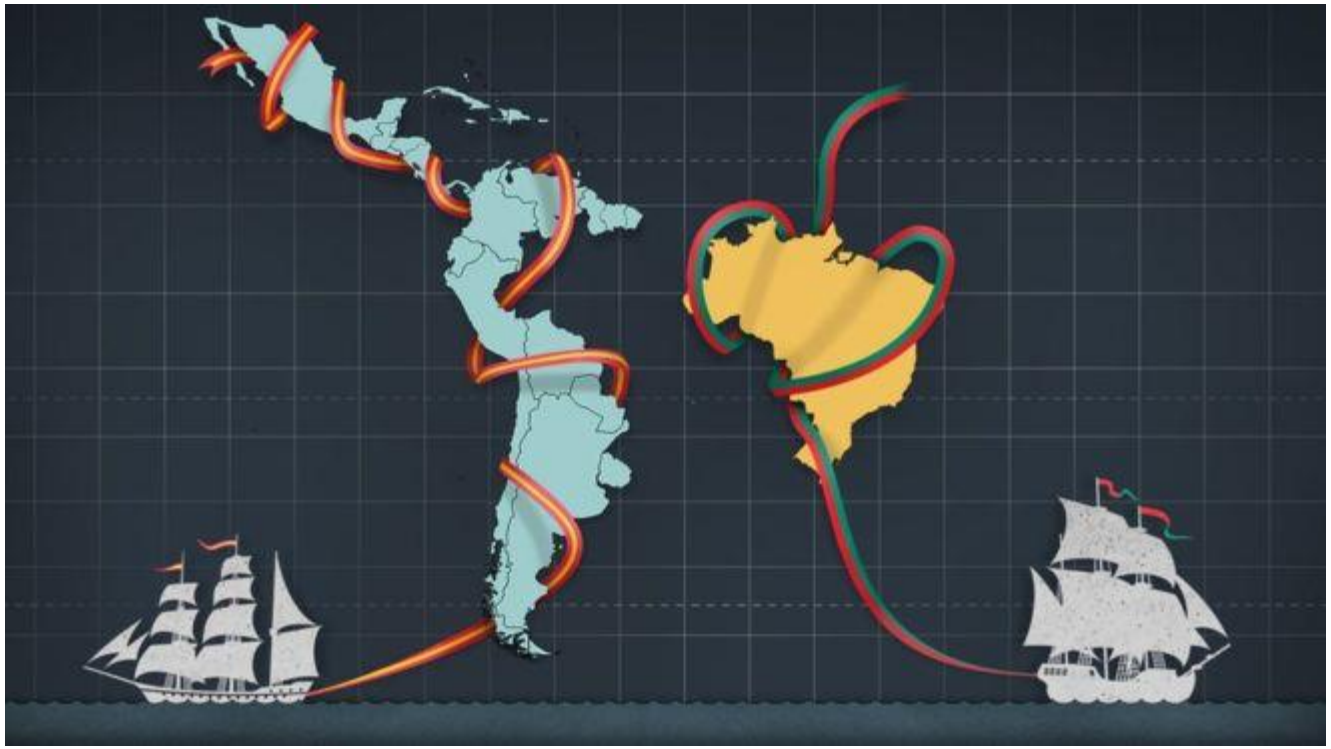
# Spanish vs Portuguese Empires



# Trans-Atlantic Slave Trade – 1500-1866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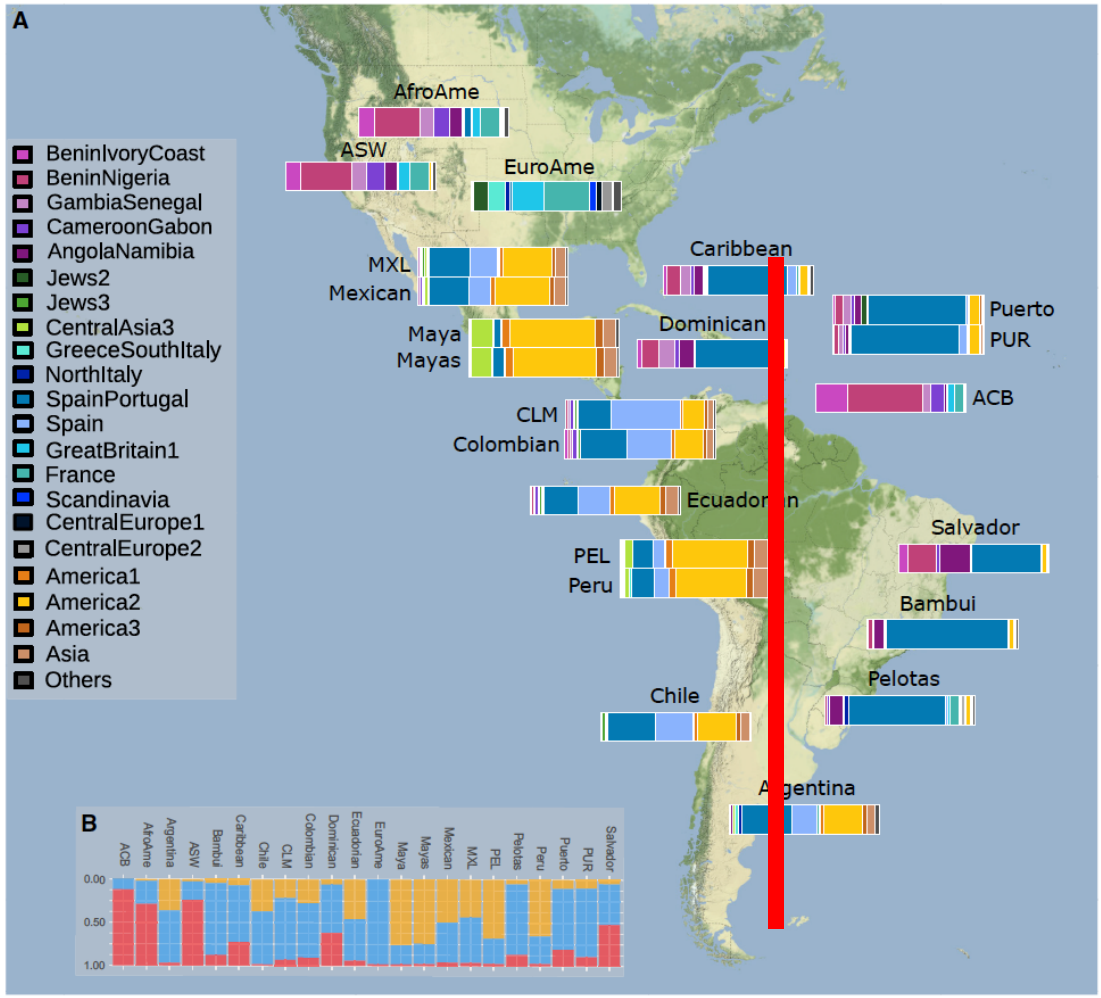
# Highly Complex Ancestral Composition of American Populations

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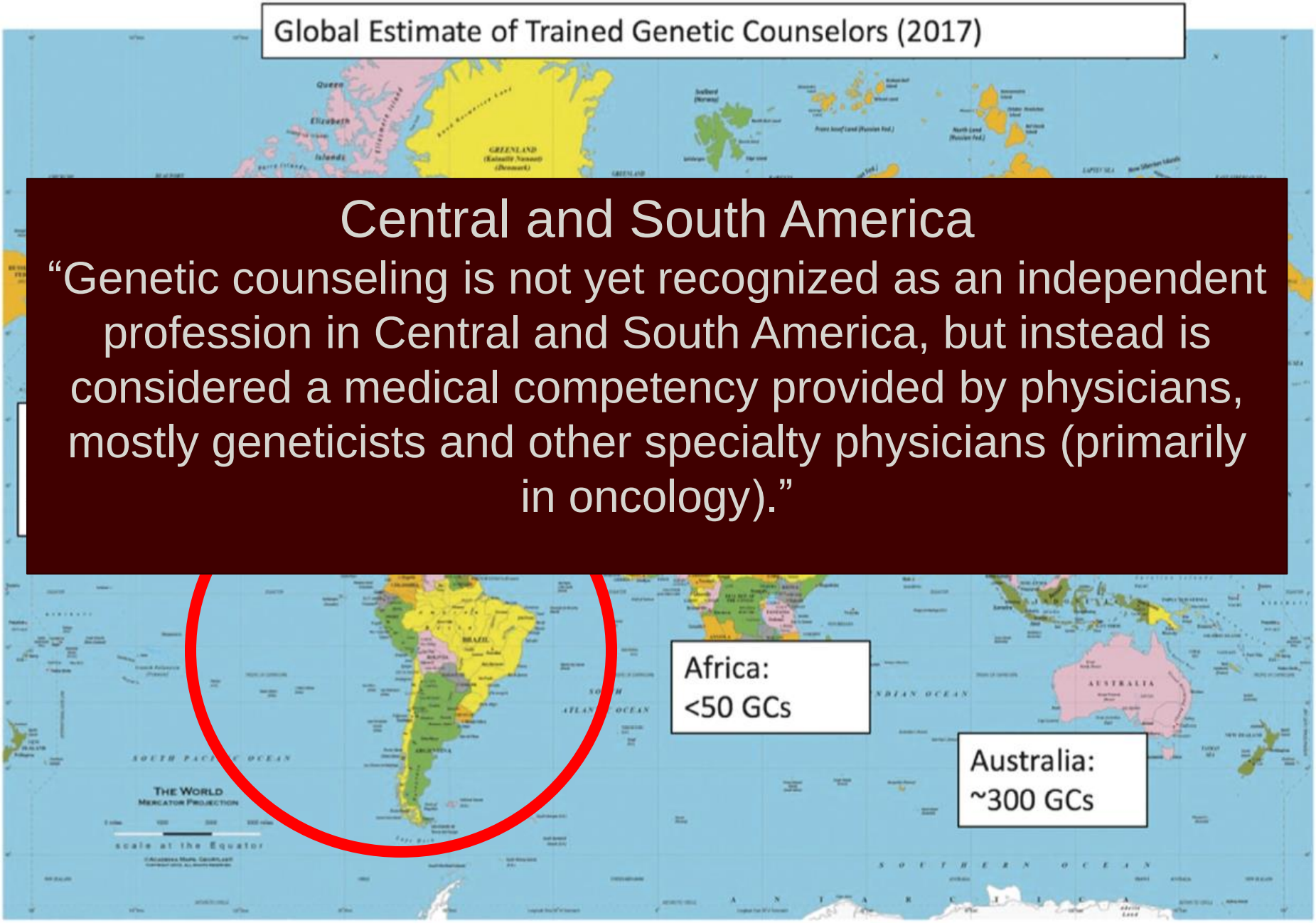
Global Estimate of Trained Genetic Counselors (2017)
Central and South America
“Genetic counseling is not yet recognized as an independent profession in Central and South America, but instead is considered a medical competency provided by physicians, mostly geneticists and other specialty physicians (primarily in oncology).”
Africa:
<50 GCs
Australia:
~300 GCs

# *BRCA1* and *BRCA2*

The prevalence and spectrum of germline mutations in BRCA1 and BRCA2 have been reported in single populations, with the majority of reports focused on Caucasians in Europe and North America.

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# The scope of BRCA1 and BRCA2 mutations in Latin American countries.


5 Countries with BRCA1/2 studies

4 Countries with BRCA1/2 and other susceptibility mutations studies

1 Countries with other susceptibility mutations studies

2 Countries without BRCA1/2 and other susceptibility mutations studies

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Jara L et al. Biol Res 50, 35 (2017).

# BRCA1/2 mutation prevalence in selected countries in Latin America

| Country | Cohort selecting criteria | *BRCA* prevalence |
|---|---|---|
| Argentina[68,69] | Personal or FH of BC/OC<br>BC/OC in ≤ 40 y); FH; or AJ ancestry | 19.04-28.3% |
| Bahamas[20,21] | BC<br>Unaffected women with FH of BC/OC | 23%<br>2.8% |
| Brazil[70-75] | BC unselected cases<br>FH of BC/OC<br>BC with FH<br>HBOC criteria<br>OC unselected | 2.3%<br>3.4%<br>13%<br>2.8-26%<br>35.5% |
| Chile[76-79] | BC/OC with FH | 7.1-20.4% |
| Colombia[29,30,45] | BC patients<br>BC/OC families<br>OC patients | 1.2%<br>24.5%<br>15.6% |
| Costa Rica[22] | BC with FH | 4.5% |
| Cuba[23] | BC patients | 2.6% |
| Mexico[43,46,80-82] | BC/OC unselected cases<br>Early BC<br>TNBC | 4.3-28%<br>6%<br>23% |
| Peru[44] | Unselected cohort | 5% |
| Puerto Rico[24] | BC and unaffected individuals with FH | 47.8% |
| Uruguay[25] | BC with FH | 17% |
| Venezuela[83] | BC cases with FH, early onset or bilateral BC | 17.2% |
| US Hispanics[10] | Unselected BC patients | 1.2-4.9% |

BC: breast cancer; FH: family history; HBOC: hereditary breast and ovarian cancer; OC: ovarian cancer; AJ: Ashkenazi Jewish; TNBC: triple negative breast cancer; y: years.

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# Common *BRCA1* Mutations by Country

The Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA

- 18,435 families with *BRCA1* mutations
- 11,351 families with *BRCA2* mutations
- 69 centers in 49 countries on 6 continents

| | | | | Five Most Common Mutations (Number Observed) | | | | |
|---|---|---|---|---|---|---|---|---|
| Conti-nent | Country | Families | Unique Mutations | 1 | 2 | 3 | 4 | 5 |
| South/Central America | Argentina | 89 | 35 | c.68_69del(22) | c.5266dup(12) | c.211A>G(11) | c.181T>G(6) | c.427G>T(3) |
| | Brazil | 101 | 39 | c.5266dup(31) | c.3331_3334del(18) | c.135−?_441+?del(4) | c.1687C>T(4) | c.3916_3917del(3) |
| | Colombia | 55 | 2 | c.3331_3334del(36) | c.5123C>A(19) | | | |
| | Mexico | 25 | 15 | c.548−?4185+?del(8) | c.68_69del(2) | c.824_825ins10(2) | c.211A>G(2) | c.5030_5033del(1) |
| | Peru | 1 | 1 | c.4986+6T>C(1) | | | | |
| | Venezuela | 1 | 1 | c.5123C>A(1) | | | | |

Total = 272 families

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# Common *BRCA2* Mutations by Country

| Continent | Country | Families | Unique Mutations | Five Most Frequently Observed Mutations (Number Observed) 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|---|
| South/Central America | Argentina | 49 | 21 | c.5946del(18) | c.2808_2811del(5) | c.6037A>T(4) | c.9026_9030del(2) | c.5645C>G(2) |
| | Brazil | 47 | 33 | c.2T>G(5) | c.2808_2811del(4) | c.156_157insAlu(4) | c.6405_6409del(3) | c.1138del(2) |
| | Colombia | 19 | 4 | c.2808_2811del(15) | c.5851_5854del (2) | c.6275_6276del(1) | c.93G>A(1) | |
| | Costa Rica | 1 | 1 | c.9235del(1) | | | | |
| | Honduras | 1 | 1 | c.7558C>T(1) | | | | |
| | Mexico | 6 | 6 | c.3264dup (1) | c.6275_6276del (1) | c.2224C>T (1) | c.5542del (1) | c.6502G>T (1) |

Total = 123 families

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# Ten Most Frequently Observed Mutations

| | Mutation Rank | South/Central America |
|---|---|---|
| *BRCA1* | 1 | c.3331_3334del (20%) |
| | 2 | c.5266dup(16%) |
| | 3 | c.68_69del(9%) |
| | 4 | c.5123C>A(8%) |
| | 5 | c.211A>G(5%) |
| | 6 | c.181T>G(3%) |
| | 7 | c.548−?_4183+8?del(3%) |
| | 8 | c.1687C>T(2%) |
| | 9 | c.135−?_441+?del(2%) |
| | 10 | c.5030_5033del (2%) |
| Families | | 271 |
| Unique Mutations | | 75 |

| | Mutation Rank | South/Central America |
|---|---|---|
| *BRCA2* | 1 | c.2808_2811del (11%) |
| | 2 | c.5946del(9%) |
| | 3 | c.2T>G(2%) |
| | 4 | c.156_157insAlu (2%) |
| | 5 | c.6037A>T(2%) |
| | 6 | c.6405_6409del(3) |
| | 7 | c.5645C>G(1%) |
| | 8 | c.658_659del(1%) |
| | 9 | c.7180A>T(1%) |
| | 10 | c.5851_5854del (1%) |
| Families | | 222 |
| Unique Mutations | | 58 |

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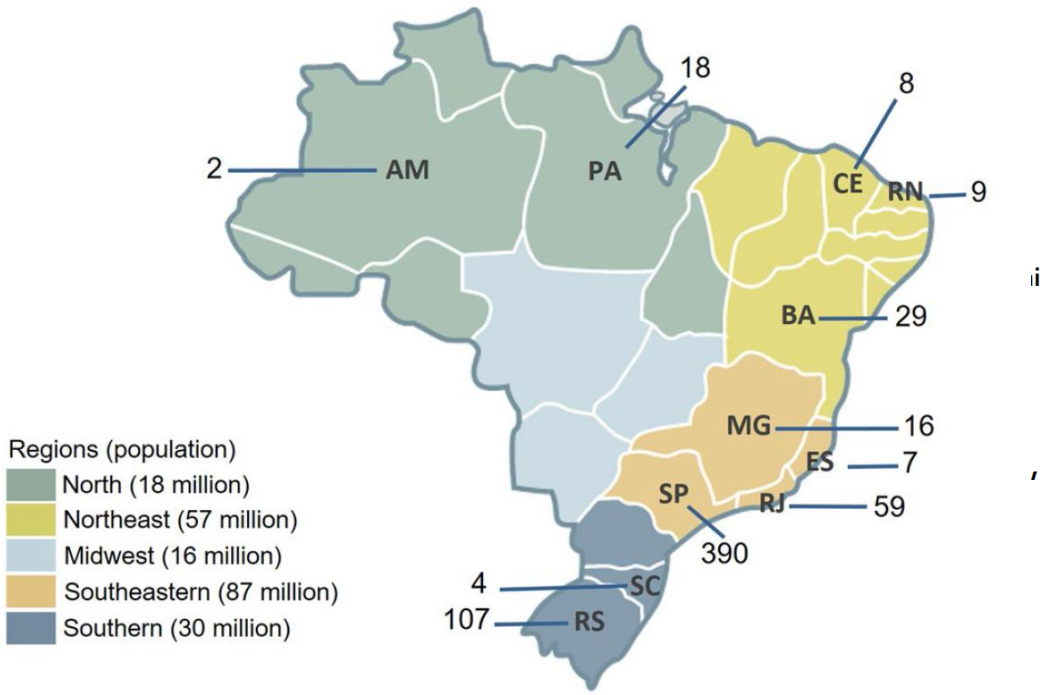


649 probands with (likely) pathogenic variants
28 public and private health care centers
distributed across 11 Brazilian States

Int J Sci Rep. 2018;4(1):9188.

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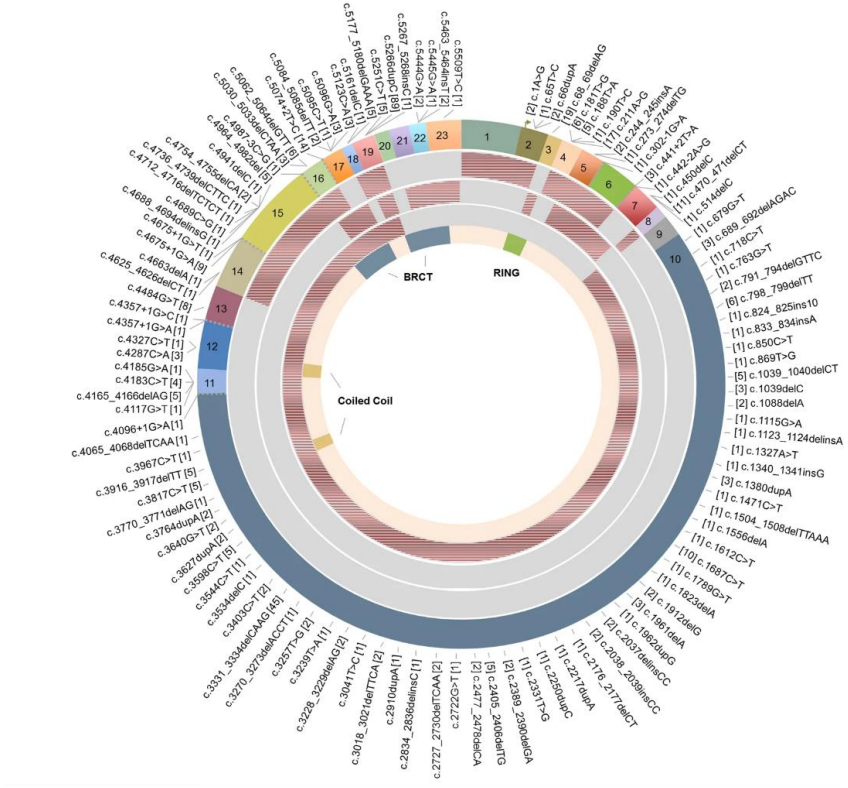
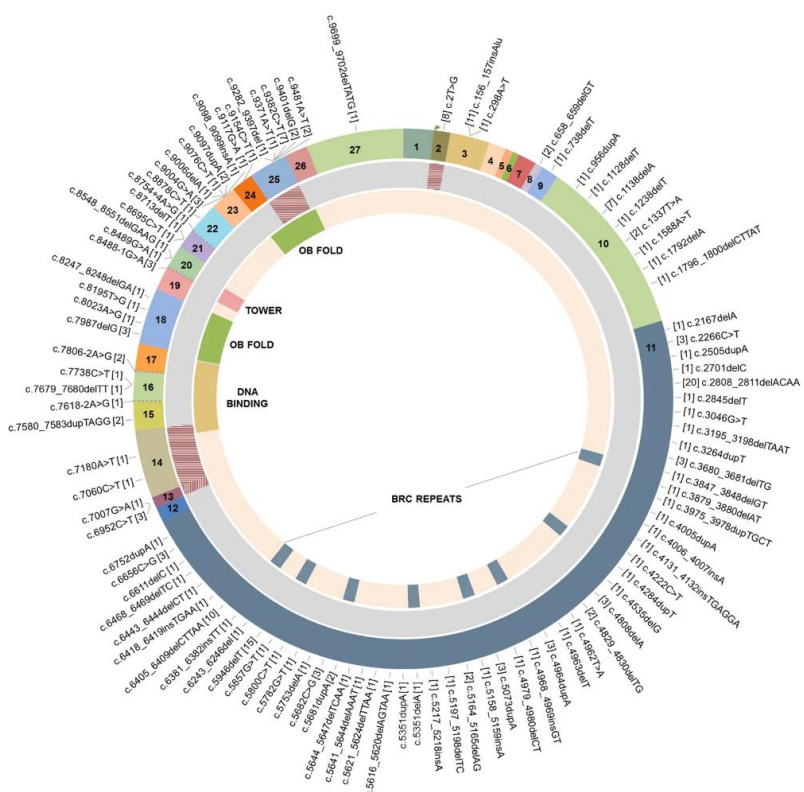
# Circos plot showing the distribution of all reported *BRCA1* and *BRCA2* mutations.




*BRCA1*
126 distinct mutations
441 unrelated individuals.




*BRCA2*
103 distinct mutations
208 unrelated individuals.

Int J Mol Sci. 2018 Jun 15;8(1):9188.

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# Most frequent reported mutations

## *BRCA1*

| Mutations identified in three or more probands (N = 33; 73.4%), N and (%) | | |
|---|---|---|
| c.5266dupC | 89 | (20.2) |
| c.3331_3334delCAAG | 45 | (10.2) |
| c.68_69delAG | 19 | (4.3) |
| c.211A>G | 17 | (3.9) |
| c.5074 + 2T>C | 14 | (3.2) |
| c.470_471delCT | 11 | (2.5) |
| c.1687C>T | 10 | (2.3) |
| c.4675+1G>A | 9 | (2.0) |
| c.4484G>T | 8 | (1.8) |
| c.181T>G | 6 | (1.4) |
| c.798_799delTT | 6 | (1.4) |
| c.5062_5064delGTT | 6 | (1.4) |

## *BRCA2*

| Mutations identified in three or more probands (N = 18; 53.4%), N and (%) | | |
|---|---|---|
| c.2808_2811delACAA | 20 | (9.6) |
| c.5946delT | 15 | (7.2) |
| c.156_157insAlu | 11 | (5.3) |
| c.6405_6409delCTTAA | 10 | (4.8) |
| c.2T>G | 8 | (3.8) |
| c.1138delA | 7 | (3.4) |
| c.9382C>T | 7 | (3.4) |
| c.2266C>T | 3 | (1.4) |
| c.3680_3681delTG | 3 | (1.4) |
| c.4808delA | 3 | (1.4) |
| c.4964dupA | 3 | (1.4) |
| c.5073dupA | 3 | (1.4) |

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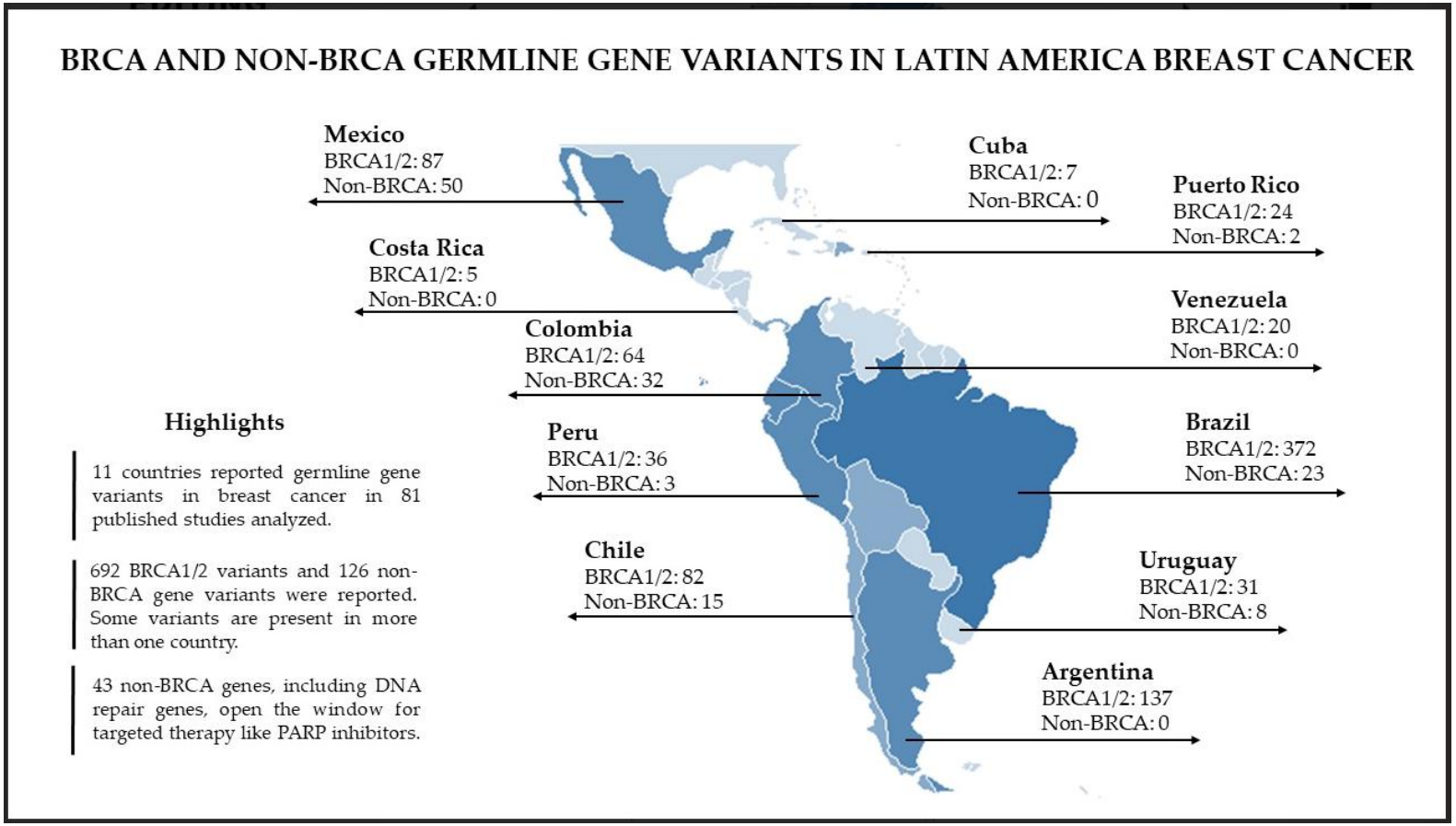
# BRCA and non-BRCA genes papers in Latin America

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# BRCA and non-BRCA genes papers in Latin America

| | Country | Total Retrieved Papers [1] | Germline Data [2] | BRCA1/2 Papers | Non-BRCA Papers | Total Papers | References |
|---|---|---|---|---|---|---|---|
| 1 | Brazil | 3290 | ✔ | 13 | 19 | 32 | [34–65] |
| 2 | Chile | 455 | ✔ | 7 | 7 | 14 | [66–79] |
| 3 | Mexico | 2014 | ✔ | 8 | 4 | 12 | [80–91] |
| 4 | Colombia | 274 | ✔ | 5 | 1 | 6 | [92–97] |
| 5 | Argentina | 893 | ✔ | 4 | | 4 | [98–101] |
| 6 | Peru | 161 | ✔ | 2 | 1 | 3 | [102–104] |
| 7 | Puerto Rico | 253 | ✔ | 2 | 1 | 3 | [105–107] |
| 8 | Uruguay | 126 | ✔ | 3 | | 3 | [108–110] |
| 9 | Costa Rica | 56 | ✔ | 2 | | 2 | [111,112] |
| 10 | Cuba | 142 | ✔ | 1 | | 1 | [113] |
| 11 | Venezuela | 76 | ✔ | 1 | | 1 | [114] |

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# Detection of inherited mutations in Brazilian breast cancer patients using multi-gene panel testing

- Nationwide sample of 1662 Brazilian patients with breast cancer referred for hereditary cancer panel testing at a single clinical diagnostic laboratory from 2015 through 2017
- NGS panels with 21–39 cancer susceptibility genes

  APC, ATM, BARD1, BLM, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EGFR, EPCAM, FANCC, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, PALB2, PIK3CA, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, RB1, RECQL, RET, STK11, TP53, WT1

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# Detection of inherited mutations in Brazilian breast cancer patients using multi-gene panel testing

## Results

- In total, 323 (20%) participants carried germline pathogenic mutations
  - 161 (10%) in *BRCA1/2*
  - 162 (9%) in other cancer predisposition genes
- A total of 766 individuals had 1 or more VUS (46%)

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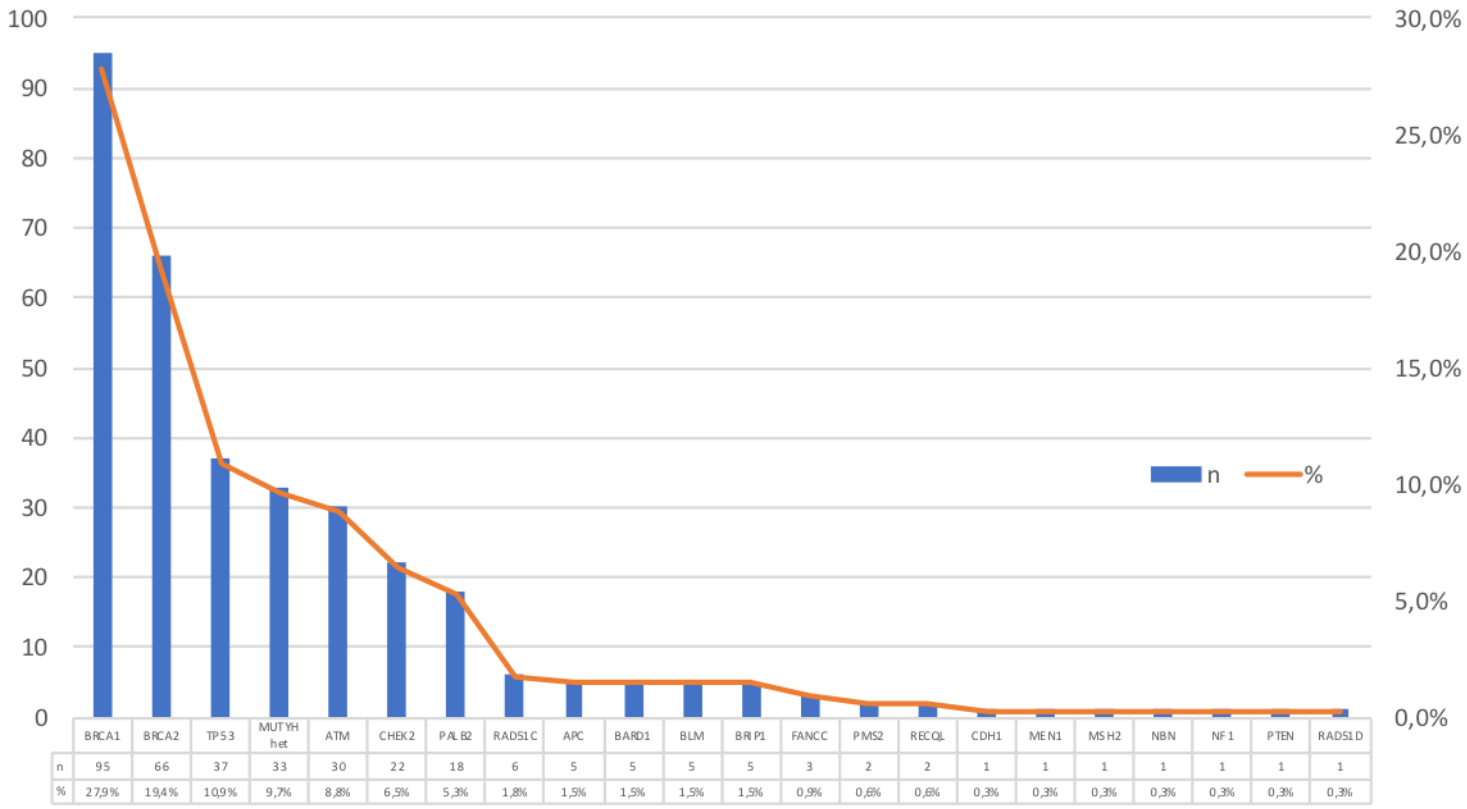
# Mutation spectrum of pathogenic and likely pathogenic variants




| | BRCA1 | BRCA2 | TP53 | MUTYH het | ATM | CHEK2 | PALB2 | RAD51C | APC | BARD1 | BLM | BRIP1 | FANCC | PMS2 | RECQL | CDH1 | MEN1 | MSH2 | NBN | NF1 | PTEN | RAD51D |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n | 95 | 66 | 37 | 33 | 30 | 22 | 18 | 6 | 5 | 5 | 5 | 5 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| % | 27,9% | 19,4% | 10,9% | 9,7% | 8,8% | 6,5% | 5,3% | 1,8% | 1,5% | 1,5% | 1,5% | 1,5% | 0,9% | 0,6% | 0,6% | 0,3% | 0,3% | 0,3% | 0,3% | 0,3% | 0,3% | 0,3% |

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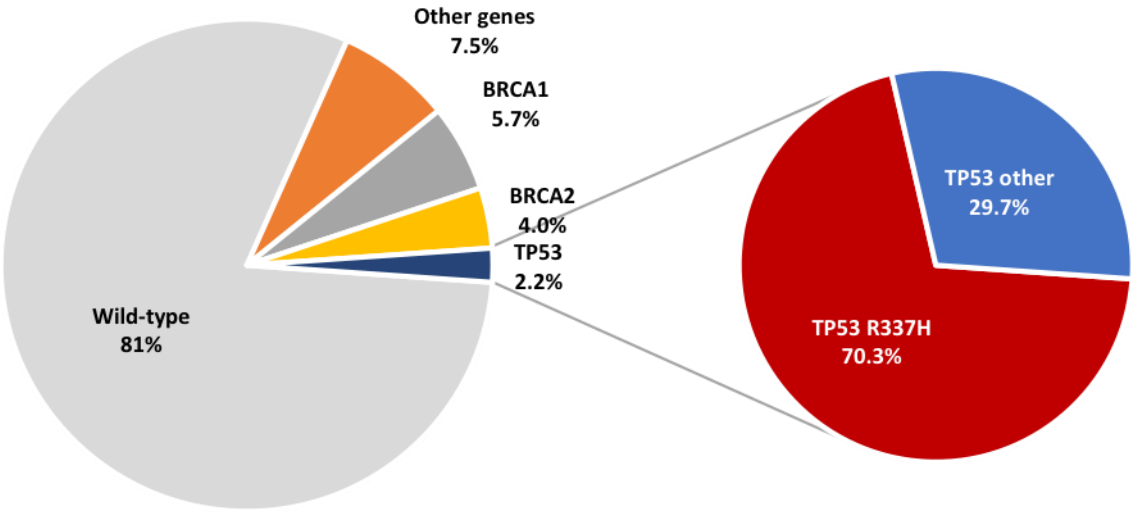
# Contribution of TP53 mutation in Brazilian breast cancer patients (n = 1,662)

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# Most Brazilian patients with TP53 germline mutation have c.1010G>A (p.Arg337His)

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Available online at www.sciencedirect.com

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Cancer Letters 245 (2007) 96–102

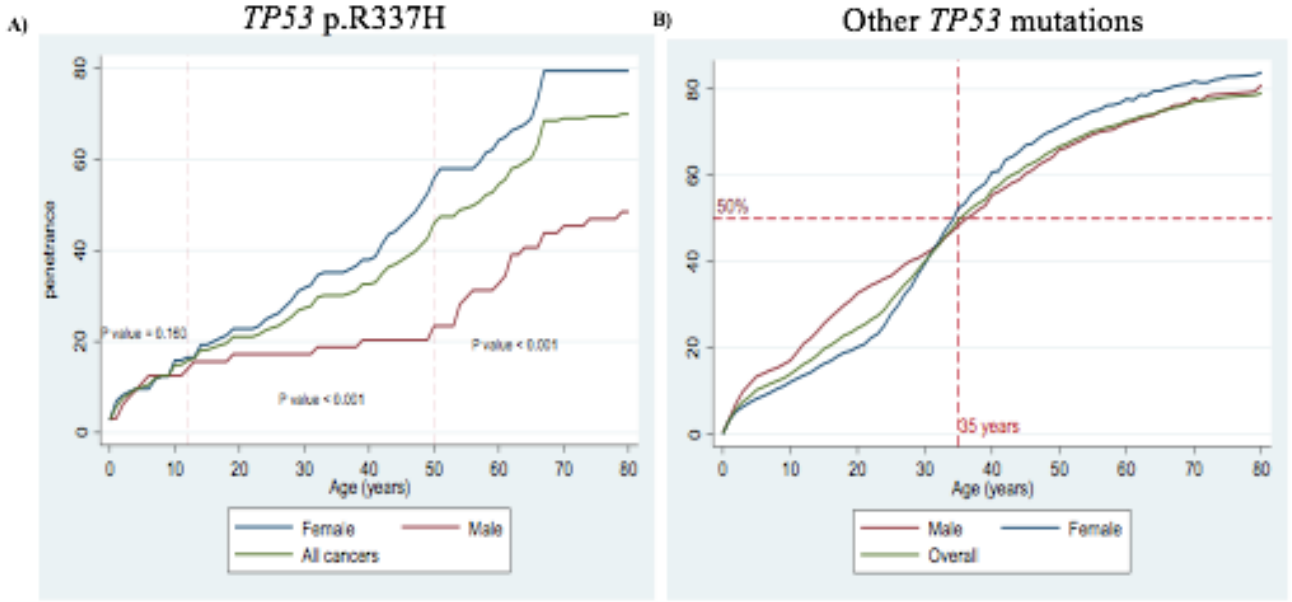
CANCER Letters

www.elsevier.com/locate/canlet

## The *TP53* mutation, R337H, is associated with Li-Fraumeni and Li-Fraumeni-like syndromes in Brazilian families

Maria Isabel Waddington Achatz [a,b], Magali Olivier [c], Florence Le Calvez [c], Ghyslaine Martel-Planche [c], Ademar Lopes [d], Benedito Mauro Rossi [d], Patricia Ashton-Prolla [e,f], Roberto Giugliani [e,f], Edenir Inez Palmero [f], Fernando Regla Vargas [g], José Claudio Casali Da Rocha [b], Andre Luiz Vettore [a], Pierre Hainaut [c,*]

# Lifetime cancer risk




- **The overall penetrance in p.R337H carriers was 27% at 30 years, 55% at 60 years**.
- Cancer risk was comparable in the two groups before age 12 years.
- Lifetime penetrance was significantly higher in females (79%) than in males (48%) in p.R337H carriers
- Carriers of p.R337H mutation had a better overall survival rate compared other TP53 mutations carriers and to non-mutation.

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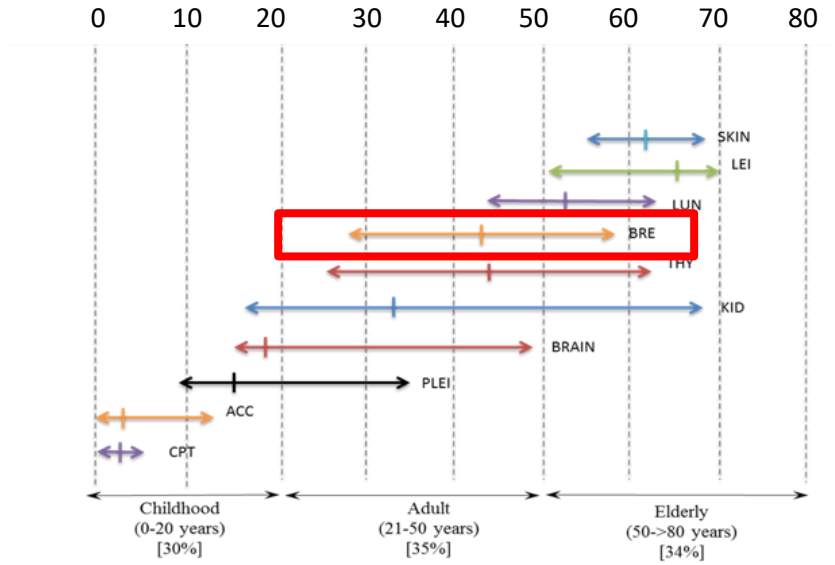
# Lifetime cancer risk

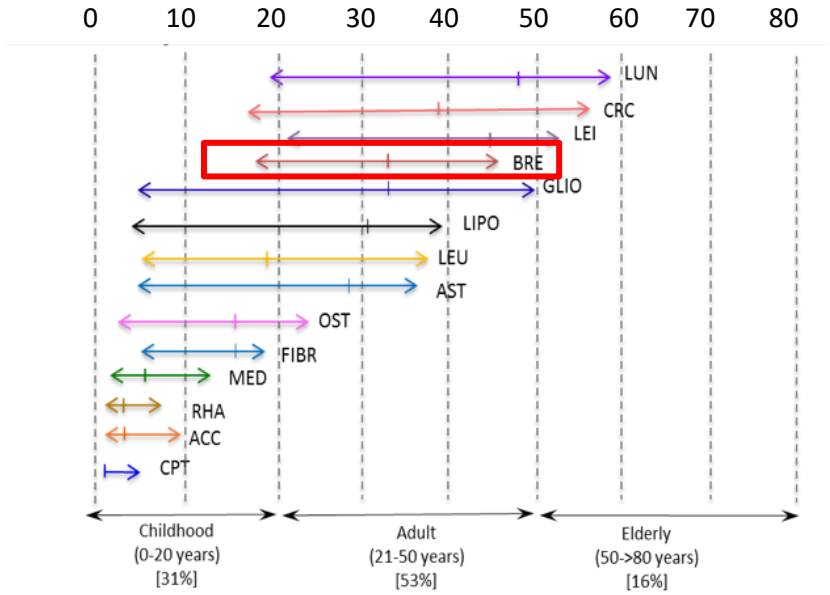
*TP53* R337H Carriers

BrCa 38-68 years




Other *TP53* mutation carriers

BrCa 18-45 years

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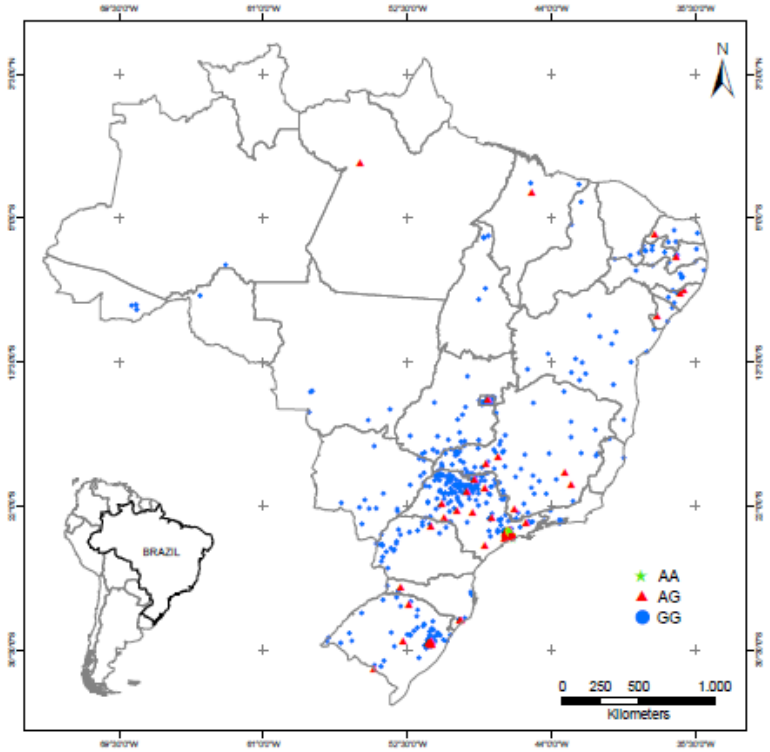
# TP53 c.1010G>A (p.Arg337His) & breast cancer




815 breast cancer pts

| Age (years) | N | N(%) carriers |
|---|---|---|
| ≤ 45 | 403 | 49 (12.1) |
| ≥ 55 | 412 | 21 (5.1) |
| Total | 815 | 70 (8.6) |

* 20% of breast cancer women ≤30yo were TP53 mutation carriers.

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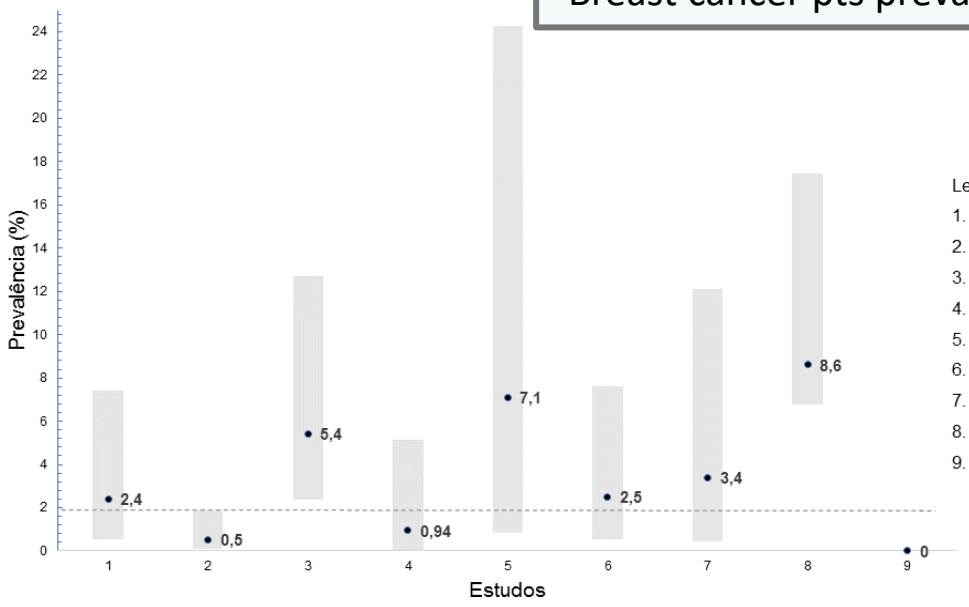
# Prevalence studies of TP53 p. (Arg337His) in breast cancer patients

Population prevalence = 0,3%
Breast cancer pts prevalence = 0,5%-8,6%




Legenda horizontal:

1. Assumpção et al 2008
2. Gomes et al 2013
3. Giacomazzi et al 2013
4. Felix et al 2014
5. Cury et al 2014
6. Silva et al 2014
7. Giacomazzi et al 2014, Brasil (grupo 1)
8. Giacomazzi et al 2014, Brasil (grupo 2)
9. Giacomazzi et al 2014, Portugal

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J Clin Oncol 31: 2619–2626.; MSc. Eriza Hahn

# Should we test all Brazilian breast cancer patients for *TP53* p.(Arg337His) ?

| | |
|---|---|
| Germline *TP53* mutation, general population | 1:3000 |
| Germline *BRCA1/BRCA2* mutation, general population | 1:600 |
| Germline *TP53* R337H mutation, general population in South Brazil | 1:300 |
| **Germline *BRCA1/BRCA2* mutation, Ashkenazi jews** | **1:50** |
| Germline *TP53* R337H mutation in Brazilian BC affected women | 1:200 – 1:12 |

R337H BC affected women in Porto Alegre = 1:43

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# Li-Fraumeni syndrome

**Adults**

General assessment
- Complete physical examination every 6 months
- Prompt assessment with primary care physician for any medical concerns

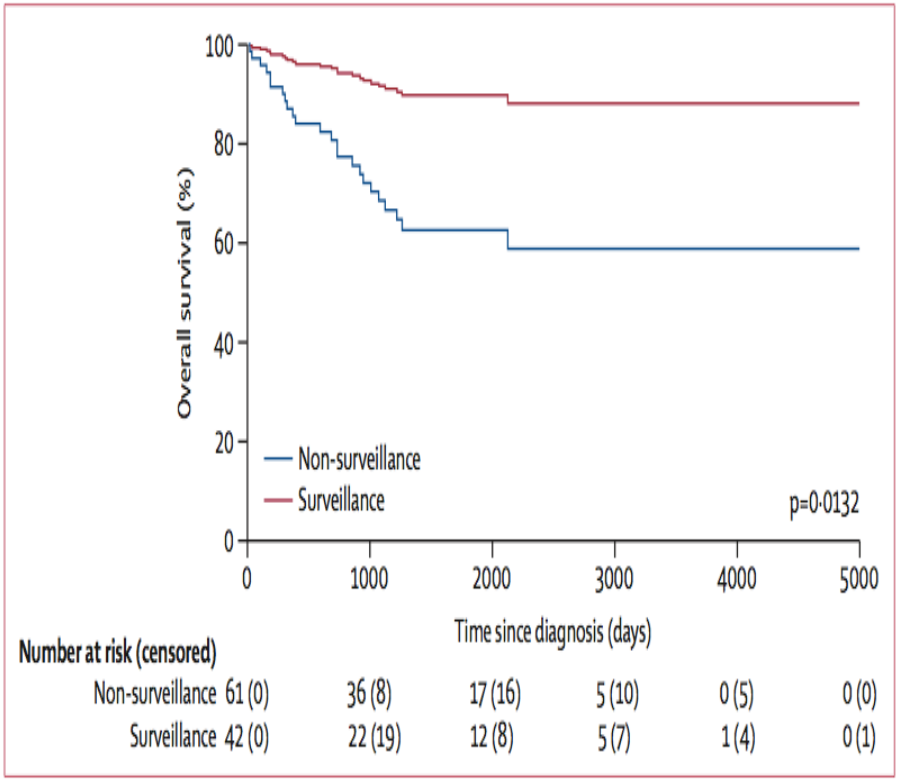
Breast cancer
- Breast awareness (age 18 years onward)
- Clinical breast examination twice a year (age 20 years onward)
- Annual breast MRI screening[c] (ages 20–75)
- Consider risk-reducing bilateral mastectomy

Brain tumor (age 18 years onward)
- Annual brain MRI (first MRI with contrast; thereafter without contrast if previous MRI normal)

Soft tissue and bone sarcoma (age 18 years onward)
- Annual WBMRI[c]
- US of abdomen and pelvis every 12 months

Gastrointestinal cancer (age 25 years onward)
- Upper endoscopy and colonoscopy every 2–5 years

Melanoma (age 18 years onward)
- Annual dermatologic examination

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Clin Cancer Res. 2017,23(11):e38-e45; Lancet Oncol 2016,17:1295-305

# Facts

- The inhabitants of Latin America represent the most genetically admixed population in the world

- There is a great need to expand hereditary cancer testing and counseling

# Barriers to adequate diagnosis and management of hereditary cancer

| Access Barriers | Education Barriers | Quality Assurance Barriers |
|---|---|---|
| Lack of a structured referral network in both public and private health care systems | Limited public awareness of genetic risk and of the benefits of GCRA | Lack of regulatory guidelines governing quality control of laboratories and genetic tests |
| Insufficient number of trained professionals who are able to recognize and provide genetic counseling to patients with a higher cancer risk | Incomplete/incorrect counseling provided by professionals with limited knowledge in the field | Lack of continued assessment of the quality of the clinical services provided in cancer genetics |
| Absence of genetic testing in the public system and limited access for coverage in the private setting[a] | Limited knowledge of HBOC syndrome and tests among health care professionals at all levels of care | Lack of adequate research budget for epidemiologic studies to delineate hereditary cancer in the country |
| Limited availability to genetic counseling in both public and private systems | Reluctance of at-risk patients and family members to seek genetic testing and counseling | Lack of funding to develop innovative solutions to overcome local barriers |
| High cost of genetic tests | Cultural and religious barriers | |
| Lack of inclusion of GCRA and surveillance of patients in the national cancer policy | Patient and family fears and misconceptions | |

Abbreviations: GCRA, genetic cancer risk assessment; HBOC, hereditary breast and ovarian cancer.
[a]Patients must fulfill Agencia Nacional de Saude criteria, including the need for a prescription from a board-certified clinical geneticist to qualify for reimbursement.

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# How to overcome these barriers

- Establishment of nationwide genetic health care services
  - network of reference centers in both public and private health care systems
- Regulatory agencies should prioritize the incorporation of policies related to hereditary cancer
  - continuing professional education and periodic recertification
- Development of training program for health professionals
- Streamlined approachs should be implemented
- Government, medical societies, health care professionals, and patient organizations should support education programs to promote public awareness
- Politicians should be encouraged to pass laws protecting individuals against genetic discrimination

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# Thank You

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