Founder Mutations in the BRCA1 and BRCA2 genes in the Latin American Population - State of the art and Literature Review

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Introduction: The "founder effect" concept explains the reduced genetic variability in some populations through the theory that new populations can be formed from a reduced number of individuals, so the new population would carry only a small fraction of the genetic variability of the original population.

Hispanic/Latinos now have a complex population structure with significant genetic contributions from Indigenous Americans and European populations (mainly immigrants from the Iberian Peninsula and Southern Europe), along with West African populations that came to the Americas in the transatlantic slave route . It has been observed that the risk of breast cancer in Latin women is associated with a larger proportion of European ancestry. For every increase of 25% of European ancestry, an increase of 20% was observed in the risk of breast cancer (95% confidence interval [CI], 1.03-1.41; p = 0.019).

Purpose: The main purpose of this review is to provide an update on the state of the art in founder mutations and some recurrent mutations that have been recently described in Latin America.

Methods: A literature search was performed in the electronic databases of PUBMED, EMBASE, LILACS and BIREME using the terms BRCA1, BRCA2, Founder Mutation, Latin American Population and Hispanic. A total of 62 papers were identified, of which 38 were selected because they were considered relevant for this review.

Results: In Latin America, clear founder effects have been reported in Mexico (BRCA1 del exons 9-12), Brazil (BRCA1 5382insC, BRCA2 c.156_157insAlu), Colombia (BRCA1 3450del4, A1708E and BRCA2 3034del4) and in Latinas residing in Southern California (BRCA1 185delAG, IVS5+1G>A, S955X and R1443X) [53]. Of these, mutation BRCA1 3450del4 has also been reported in Brazil and Chile, while mutation BRCA2 3034del4 has been reported in Argentina and Peru.

These data support the idea that although most Hispanic populations are the result of a mixture between Europeans, Africans and Amerindians, the relative proportion of each genetic component varies throughout the Hispanic populations, making it necessary to identify the mutations characteristic of each population to generate mutation profiles adjusted to each one of them.

Guatemala, El Salvador, Honduras, Nicaragua, Panamá, Bolivia, Ecuador, Paraguay and Uruguay: there are no reports of population studies on mutations in BRCA1 or BRCA2 genes in these countries.

Conclusions: In Latin American countries and even among regions of the same country, there is great heterogeneity from the ancestral point of view. Therefore, the "Latinas" should not be analyzed like other population groups without taking into account their genetic ancestry. If we manage to decrease costs, screenings could be offered more widely and could cover a larger number of women. Even though BRCA1/2-founder mutations associated with increased risk of breast and other cancers have been identified in some Latin American countries, several other founder mutations may exist that have not yet been identified due to the limited number of investigations performed to date. Further studies need to be done in Latin America.

Table 1 - Recurrent and founder mutations in the BRCA1 and BRCA2 genes described in Latin America.

Country	*Recurrent Mutations in BRCA1*	*Recurrent Mutations in BRCA2*	Founder Mutations in *BRCA1*	Founder Mutations in *BRCA2*	Mutation Detection Method	Literature Reference
Argentina		3034del4	185delAG, 5382insC	6174delT	Direct DNA sequencing	Solano AR., *et al.* 2012
Brazil	185delAG, ins6Kb, 3450del4, 2156delGinsCC and c.211A>G	6633del5	5382insC	c.156_157insAlu	Polymerase chain reaction (PCR), reverse transcriptase PCR (RT-PCR), PTT, DGGE and DHPLC. All variants identified were confirmed by direct DNA sequencing.	Da Costa ECB *et al.* 2008; Gomes MC., *et al.* 2007; Machado PM., *et al.* 2007; Esteves VF., et al. 2009; Felix GES., *et al.*, 2014
Chile	185delAG, 2605delTT and 3450del4	4969insTG, 5374del4 y 6503delTT			Conformation-sensitive gel electrophoresis (SSCP). All variants identified were confirmed by direct DNA sequencing.	Jara L., *et al.,* 2006
Colombia		6076del4 6503delTT	A1708E 3450del4	3034del4	DHPLC, SSCP and PTT, followed by DNA sequencing analysis.	Torres D., *et al.,* 2007
Costa Rica		5531delTT			Only exon 10 of *BRCA1* and exons 10 and 11 of *BRCA2* were screened by PTT. All mutations were confirmed by direct sequencing.	Gutiérrez-Espeleta GA., *et al.,* 2012
Cuba		c.3394C>T			DGGE and PTT followed by DNA sequencing analysis.	Rodríguez RC., *et al.* 2008
Mexico			del exon9-12		Hispanel screening of 115 recurrent *BRCA1/2* Hispanic mutations. All mutations were confirmed by direct sequencing.	Villarreal-Garza C., *et al.* 2015
Peru	2080delA	3034del4	185delAG		Hispanel screening and direct DNA sequencing.	Abugattas J., *et al.* 2014

Figure 1- Countries with studies of founder and/or recurrent mutations in Latin America reported to date.

References

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