Global Ancestry Shapes Clinical and Genetic Profiles in an Admixed Colombian Breast Cancer Cohort.

William Mantilla[1], Yina Tatiana Zambrano-O[2,3], Laura Rey-Vargas[2,4], Diana Carolina Sierra-Diaz[5], Mauricio Lema[6], Dora Janeth Fonseca-Mendoza[5], Silvia J Serrano-Gomez, Carlos M Restrepo[5], Maria Carolina Sanabria-Salas..

1. Luis Carlos Sarmiento Angulo Center for Research and Cancer Treatment. 2. Instituto Nacional de Cancerología. 3. Universidad Nacional de Colombia. 4. Pontificia Universidad Javeriana. 5. Universidad del Rosario. 6. Clínica de Oncología Astorga.

Background

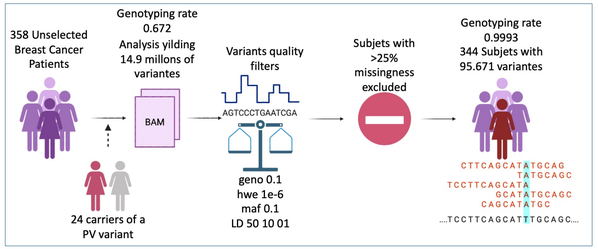
Breast cancer (BC) susceptibility is driven by a complex interplay of modifiable and non-modifiable risk factors. While the impact of BRCA1 and BRCA2 pathogenic/likely pathogenic variants (PVs) is well documented, the contribution of genetic ancestry to the distribution of PVs in BRCA1/2 and other homologous recombination repair (HRR) genes remains understudied in genetically admixed populations such as Colombians.

Methods

Whole-exome sequencing data from 358 unselected Colombian women with BC were analyzed for genetic ancestry.

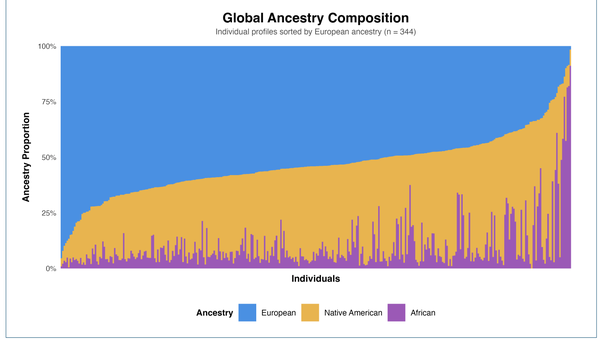
- 24 individuals were identified as carriers of PVs in BRCA1 (n=3), BRCA2 (n=10), PALB2 (n=2), ATM (n=5), CHEK2 (n=2), BARD1 (n=1), and RAD51D (n=1).

Raw BAM files underwent preprocessing, quality control, and joint genotyping, resulting in a final dataset of 344 individuals and 95,671 variants (genotyping rate: 99.93%).

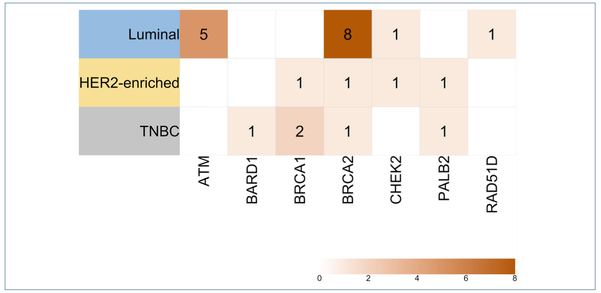


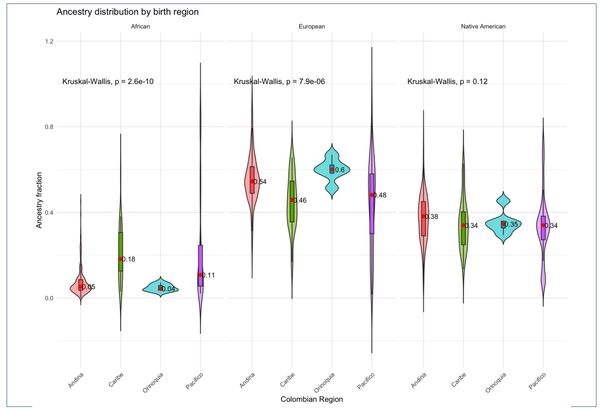
Global ancestry proportions were estimated using principal component analysis with reference populations from the 1000 Genomes and Human Genome Diversity Projects, specifically African (AFR), European (EUR), and Native American (NAM) populations. Statistical comparisons Statistical comparisons of ancestry proportions were performed across clinical variables.

Results



Global ancestry was predominantly EUR (mean ~53%), followed by NAM (~36%) and AFR (~10%). AFR ancestry was higher among cases born in the Caribbean and Pacific coast regions (18% and 11%, respectively; $p < 0.001$). EUR ancestry was higher among those from the Andean and Plains regions (54% and 60%, respectively; $p < 0.001$). The NAM component was more homogeneous across regions (34-38%). Among the 24 PV carriers, luminal subtypes predominated (63%), particularly in ATM (100%) and BRCA2 (80%) carriers.





EUR ancestry was higher in individuals with ER-positive tumors compared to ER-negative tumors (54% vs. 51%, respectively, $p < 0.05$). AFR ancestry was higher in ER-negative (8% vs. 6% in ER-positive, $p < 0.05$) and PR-negative tumors (8% vs. 5% in PR-positive, $p < 0.05$).A higher EUR component was observed among those with a positive family history (55%) ($p = 0.057$) and PVs carriers in BC-related genes (58%).

Correlation of Ancestry and Clinical, Histological and Genetic Variables

	N	EUR	p	IA	p	AFR	p
Age at diagnosis							
<50 years	150	0.54 [0.47-0.59]	0,466	0.37 [0.31-0.43]	0,535	0.06 [0.04-0.12]	0,716
>=50 years	189	0.54 [0.47-0.62]		0.36 [0.28-0.45]		0.06 [0.04-0.10]	
ER expression							
Positive	268	0.54 [0.48-0.61]	**0,038**	0.37 [0.29-0.44]	0,468	0.06 [0.04-0.09]	**0,005**
Negative	68	0.51 [0.45-0.59]		0.35 [0.28-0.44]		0.08 [0.05-0.16]	
PgR Expresion							
Positive	245	0.54 [0.47-0.61]	**0,091**	0.37 [0.29-0.44]	0,22	0.37 [0.29-0.44]	**<0.001**
Negative	91	0.52 [0.46-0.59]		0.34 [0.28-0.43]		0.34 [0.28-0.43]	

Correlation of Ancestry and Clinical, Histological and Genetic Variables

	N	EUR	p	IA	p	AFR	p
HER2 overexpression							
Positive	78	0.54 [0.46-0.59]	0,148	0.36 [0.28-0.43]	0,88	0.06 [0.04-0.13]	0,245
Negative	256	0.54 [0.47, 0.61]		0.36 [0.29-0.44]		0.06 [0.04, 0.10]	
BC Subtype							
Luminal Like	225	0.54 [0.47-0.61]	0.343	0.37 [0.29-0.45]	0.408	0.06 [0.04-0.10]	0.214
HER2 positive	78	0.54 [0.46-0.59]		0.36 [0.28-0.43]		0.06 [0.04-0.13]	
Triple Negative	31	0.54 [0.49-0.63]		0.34 [0.27-0.42]		0.08 [0.04-0.13]	
Family History of Breast or ovarian cancer							
Yes	100	0.55 [0.50-0.62]	**0.022**	0.35 [0.28-0.42]	0.187	0.06 [0.04-0.09]	0.354
No	218	0.53 [0.46-0.60]		0.37 [0.29-0.45]		0.06 [0.04-0.11]	
At least 1 PV in HR genes							
PV	18	0.58 [0.54, 0.65]	0.057	0.35 [0.25-0.40]	0.177	0.05 [0.03-0.07]	0.166
No PV	323	0.54 [0.47, 0.60]		0.37 [0.29-0.44]		0.06 [0.04-0.11]	

Two cases with CHEK2PVs [c.349A>G and c.1100delC] had 71% EUR ancestry, significantly higher than non-carriers (54%, $p < 0.05$. Four ATM PV carriers showed predominantly EUR ancestry (49-59%). The ATM splice-site variant c.5496+2_5496+5delTAAG was identified in three unrelated individuals from the Andean region—two of whom have predominantly European ancestry.

Conclusions

Our findings demonstrate significant associations between global ancestry proportions and key clinical and genetic features in an admixed Colombian BC cohort. To further elucidate the genetic and demographic factors influencing the frequency, distribution, origin, and potential impact of PVs identified in this cohort, we have initiated ongoing local ancestry estimations and haplotype analyses. This study highlights the importance of ancestry-informed analyses to improve risk stratification and guide precision medicine approaches in admixed populations.

Contact
William Armando Mantilla Dura
Luis Carlos Sarmiento Angulo Center for Cancer Research and Treatment
Website: www.cticsarmientoangulo.org Phone: +57 6017454421
Email: wmantilla@fctic.org

References

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