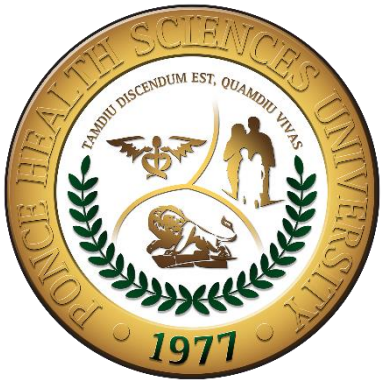
GENETIC ANCESTRY & CANCER

UPR /MD Anderson Cancer Biology Course January 10, 2015

Julie Dutil, Ph.D.

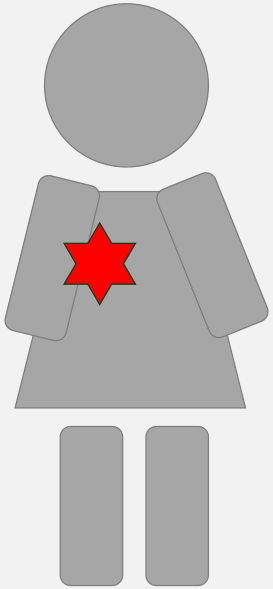


PONCE HEALTH SCIENCES UNIVERSITY

PONCE RESEARCH INSTITUTE

Cancer Genetics

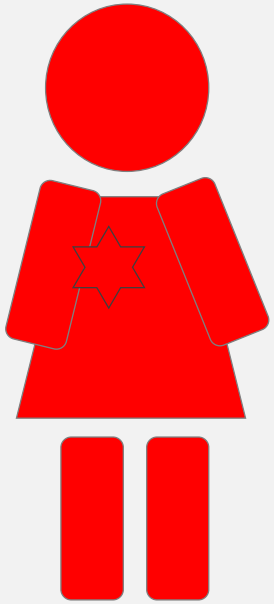
Somatic mutations



-Non-heritable;

-Determine be involved in tumor response to treatment and prognosis;

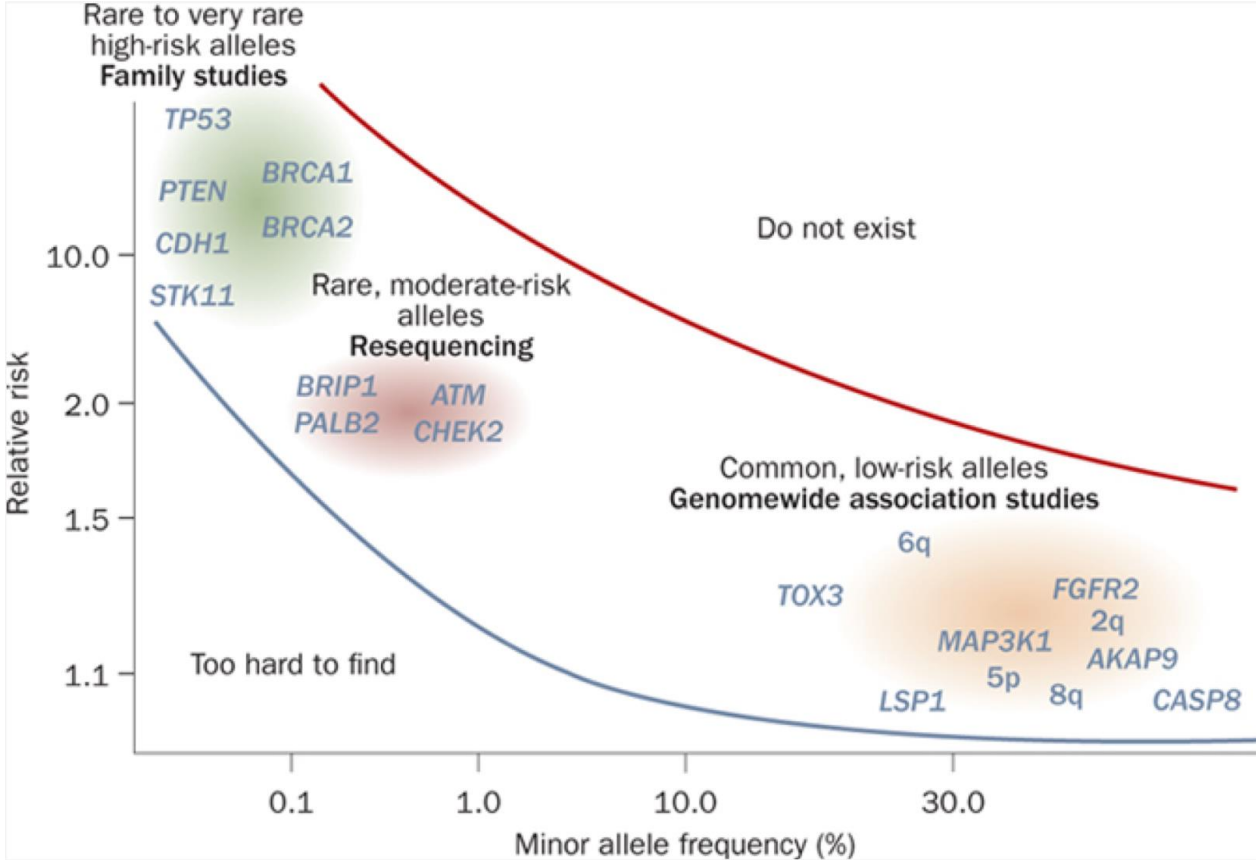
Germline mutations



-Heritable;

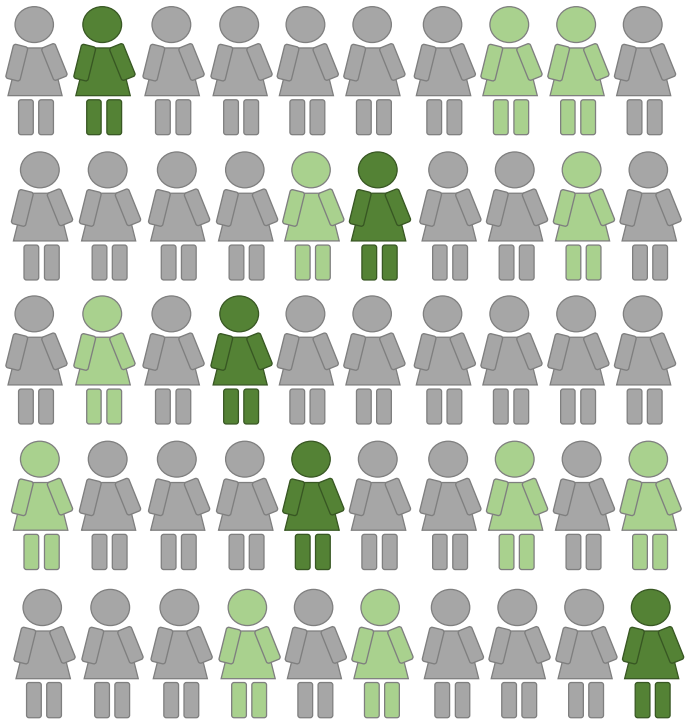
-Determine the risk that an individual will develop cancer;

Cancer genetics



Timothy J. R. Harris & Frank McCormick
Nature Reviews Clinical Oncology 7, 251-265 (May 2010)

Cancer genetics



GENETIC TESTING

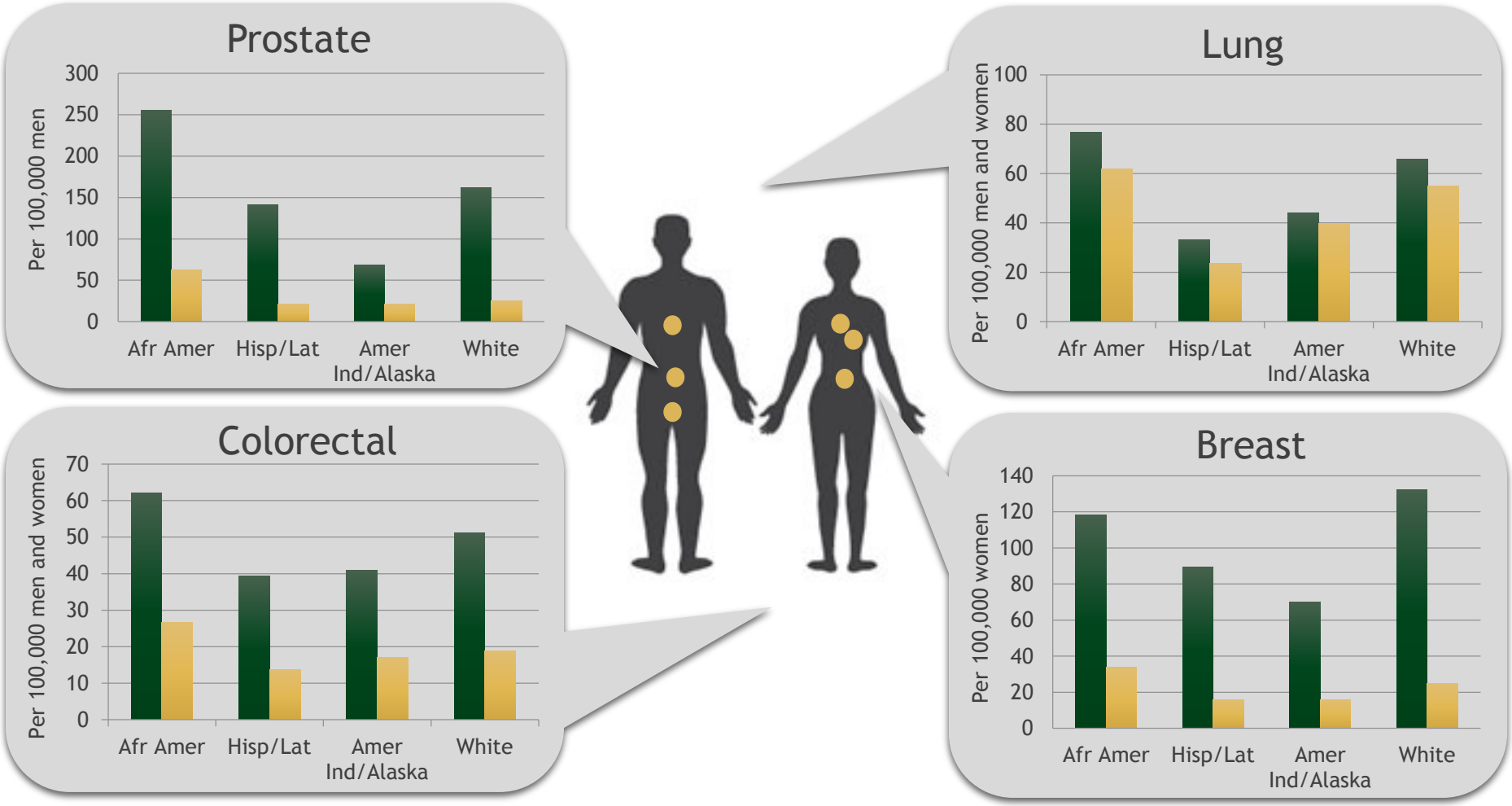
Low risk group
-Reduced surveillance

Moderate risk group
-Moderate surveillance
-Chemoprevention (?)
-Common

High risk group
-Increased surveillance
-Chemoprevention
-Preventive surgery
-Rare

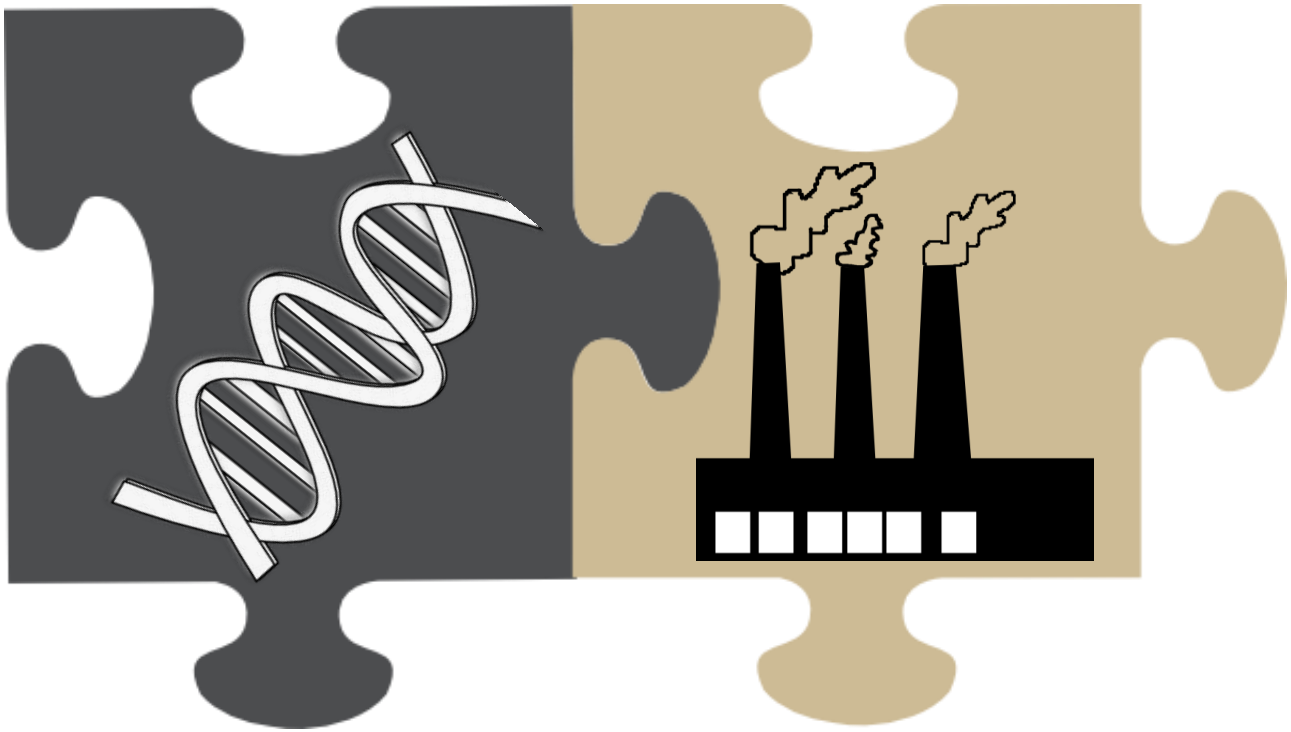
Cancer Disparities

Number of new cases (■) and deaths (■) per year;

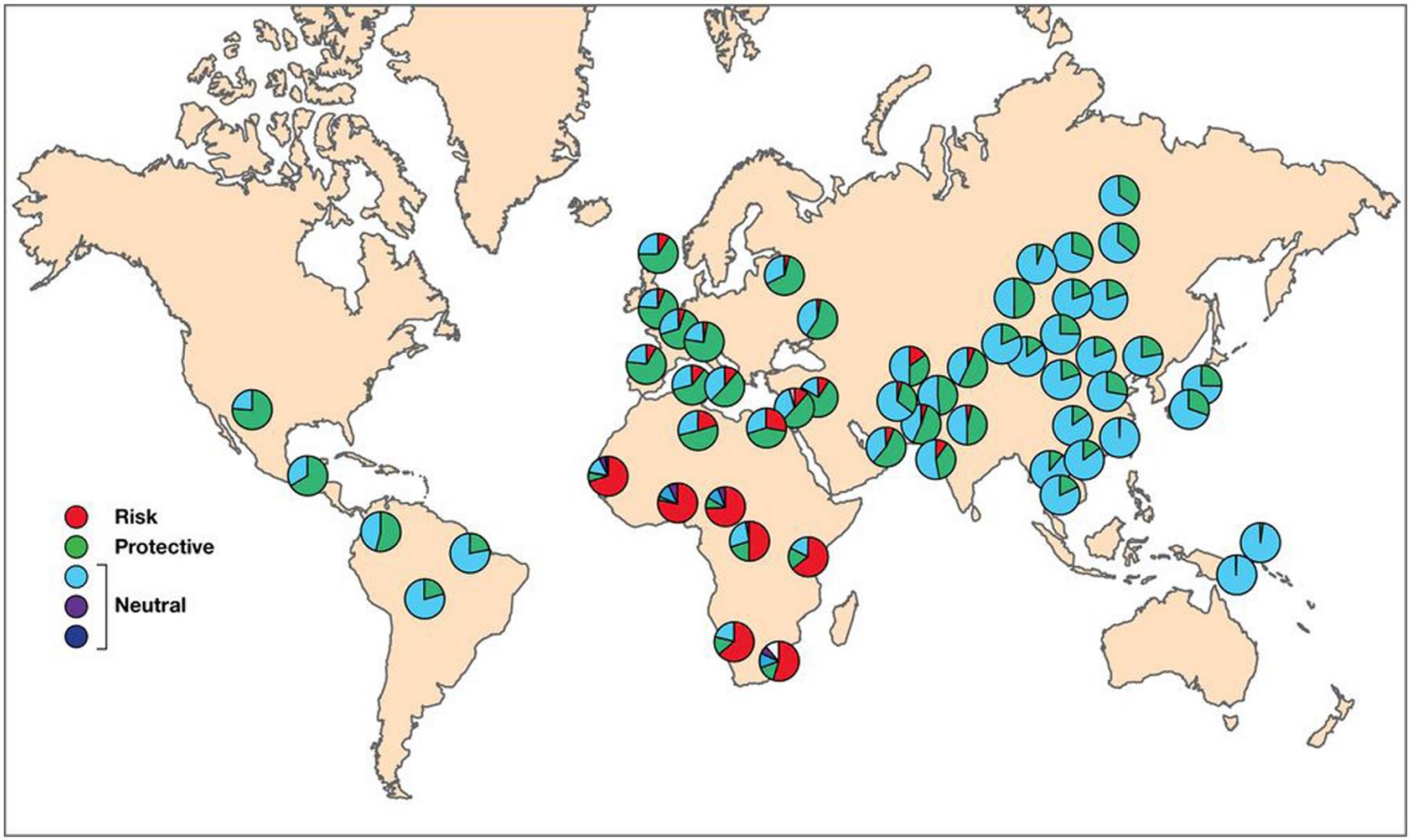


National Cancer Institute; statistics for 2000-2004, age-adjusted

Cancer Disparities



MYH9 haplotypes in kidney disease

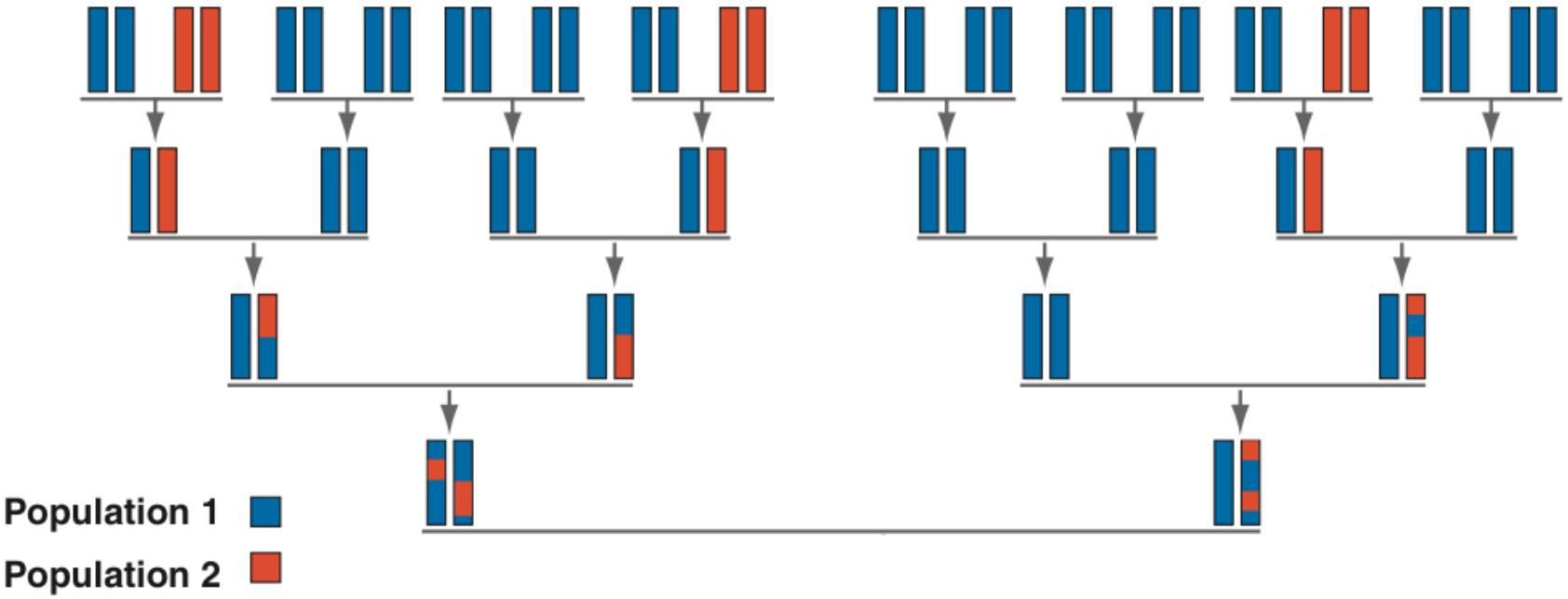


Oleksyk *et al.* (2010) PLoS One 5(7):e11474

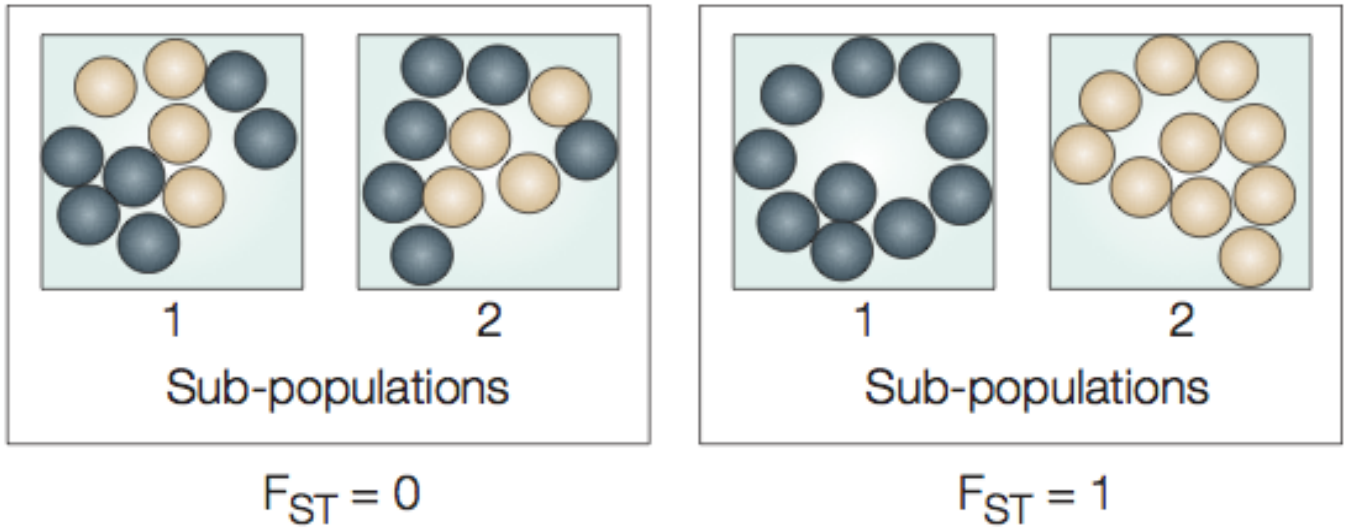
Admixed populations

In genetics, an '*admixed population*' refers to the intermixture of previously isolated populations

Admixed populations

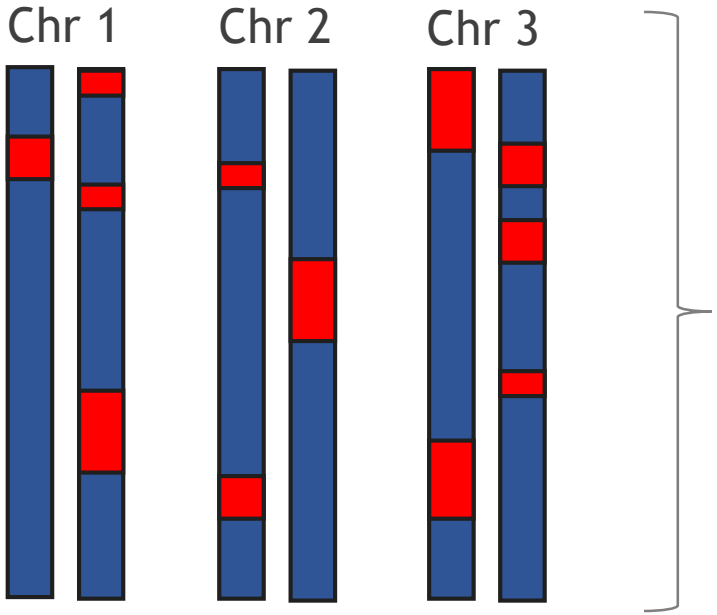


Ancestry Informative Markers (AIMs)



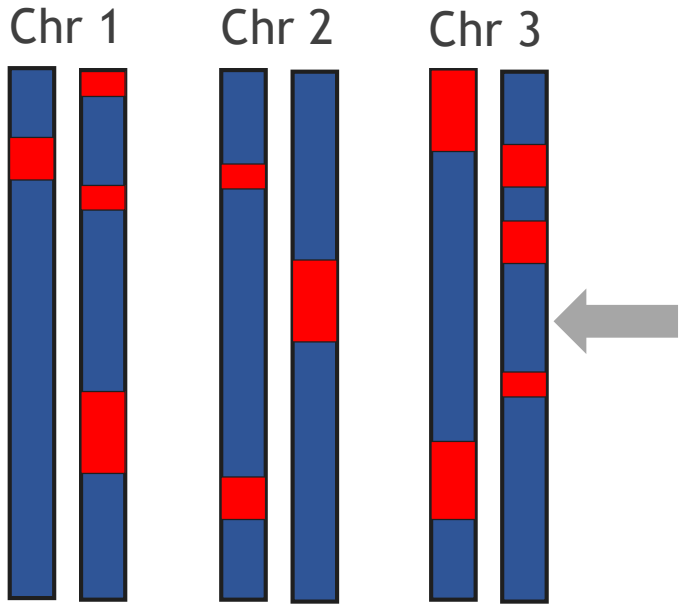
Bamshad et al. (2004) Nature Reviews Genetics 5:598

Global genetic ancestry



Proportion (%) of the genome that originated from each ancestral population that makes up an admixed population

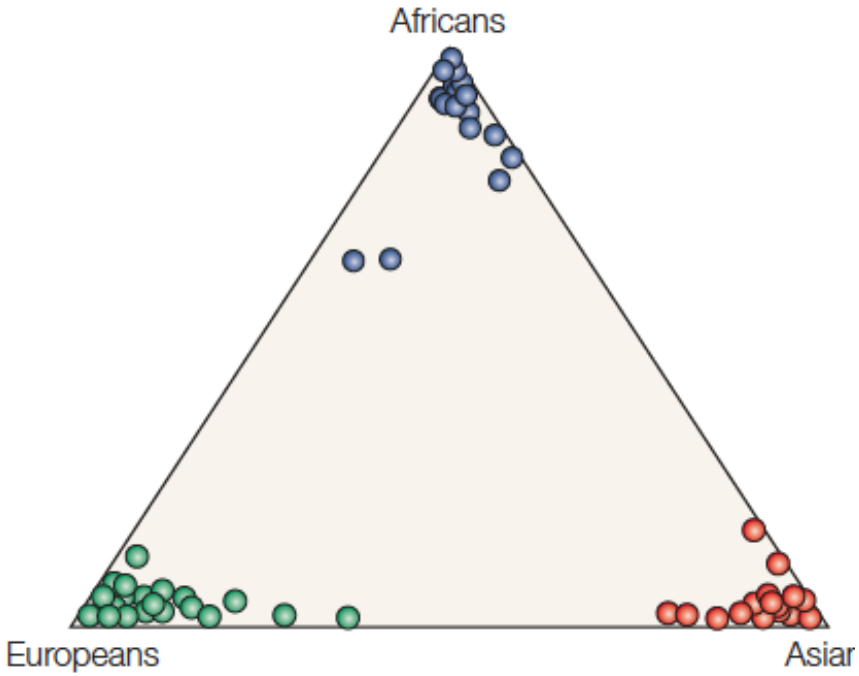
Local genetic ancestry

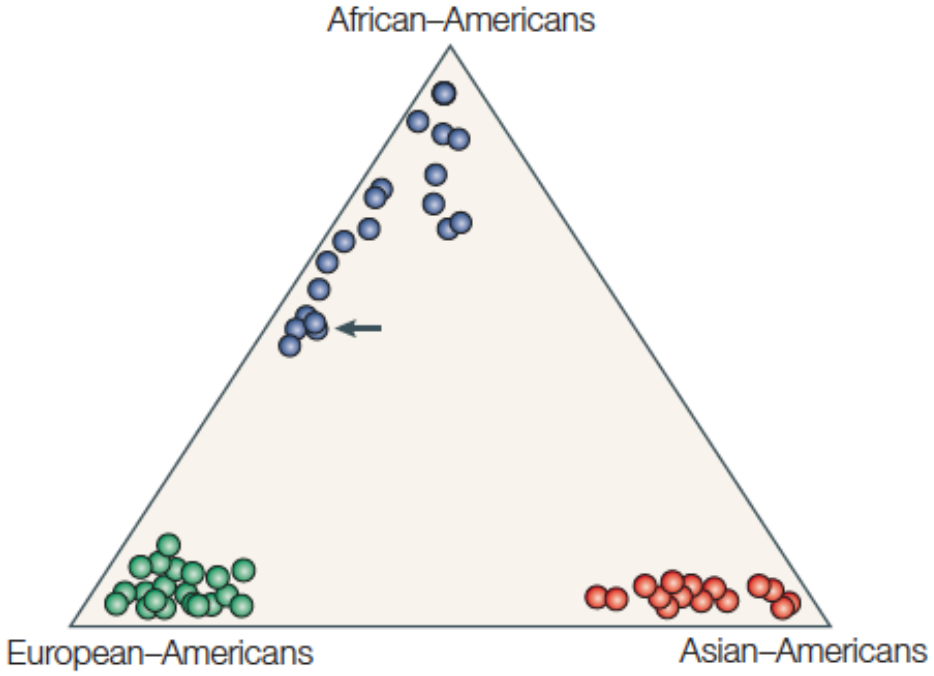


Ancestral origin of a given locus (site) in the genome

African Americans

African Americans

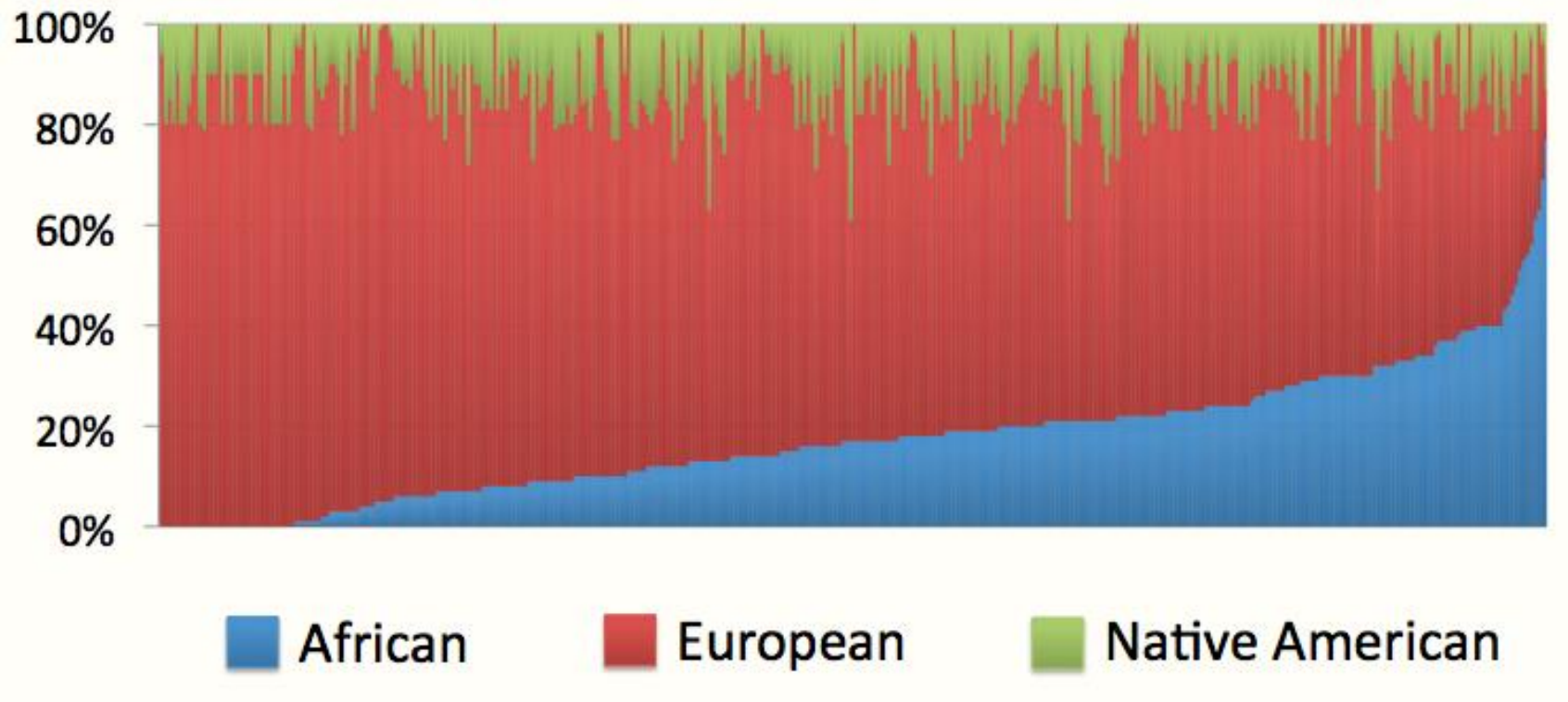




Bamshad et al. (2004) Nature Reviews Genetics 5:598

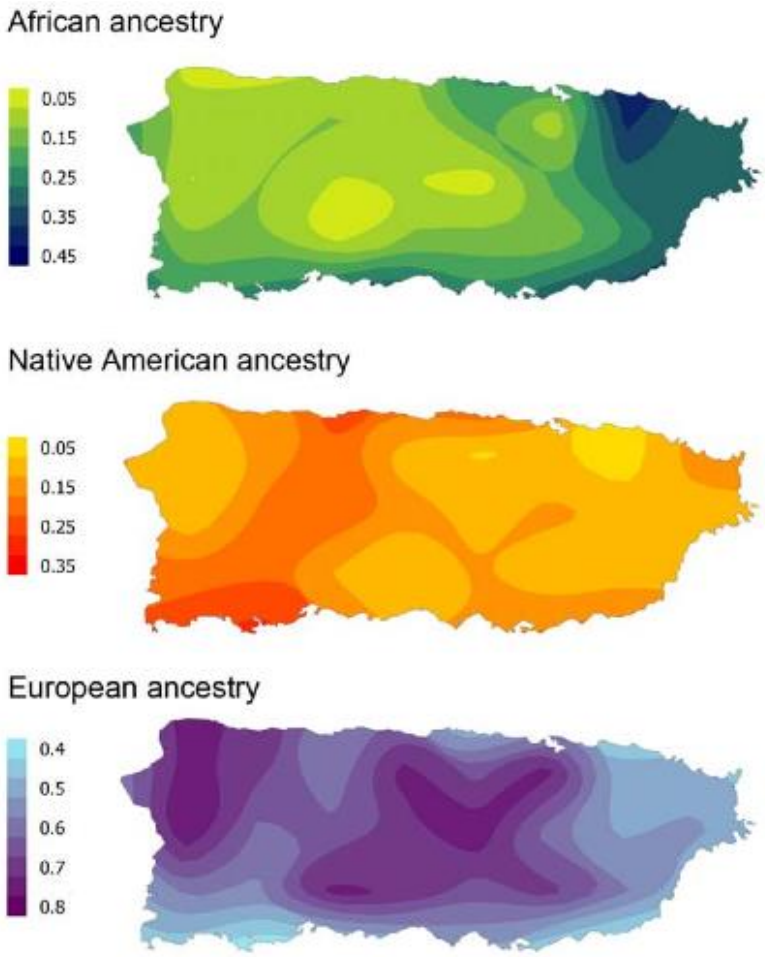
Hispanics/Latinos

Hispanics/Latinos



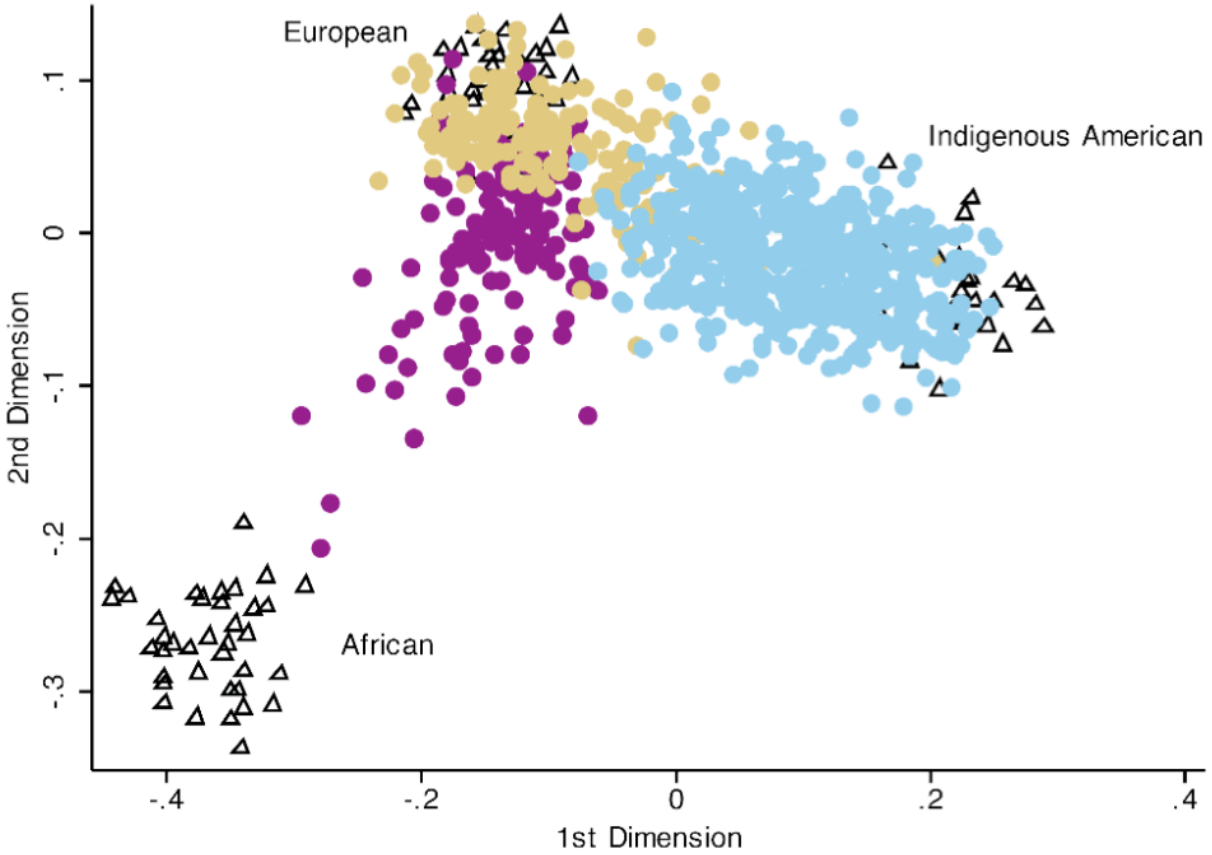
Hispanics/Latinos

Geographical
distribution
of genomic ancestry
proportions
in Puerto Rico



Via et al. (2011) PLoS ONE 6 (1) e16513

Hispanics/Latinos



From Avena S et al (2011) PLoS ONE 7(4):e34695

Global ancestry and breast cancer

- Are differences in breast cancer incidence between African American, Hispanics/Latinos and Whites be explained by genetic ancestry?

- Are differences in breast cancer tumor characteristics and prognosis between African American, Hispanics/Latinos and Whites be explained by genetic ancestry?

Global ancestry and breast cancer

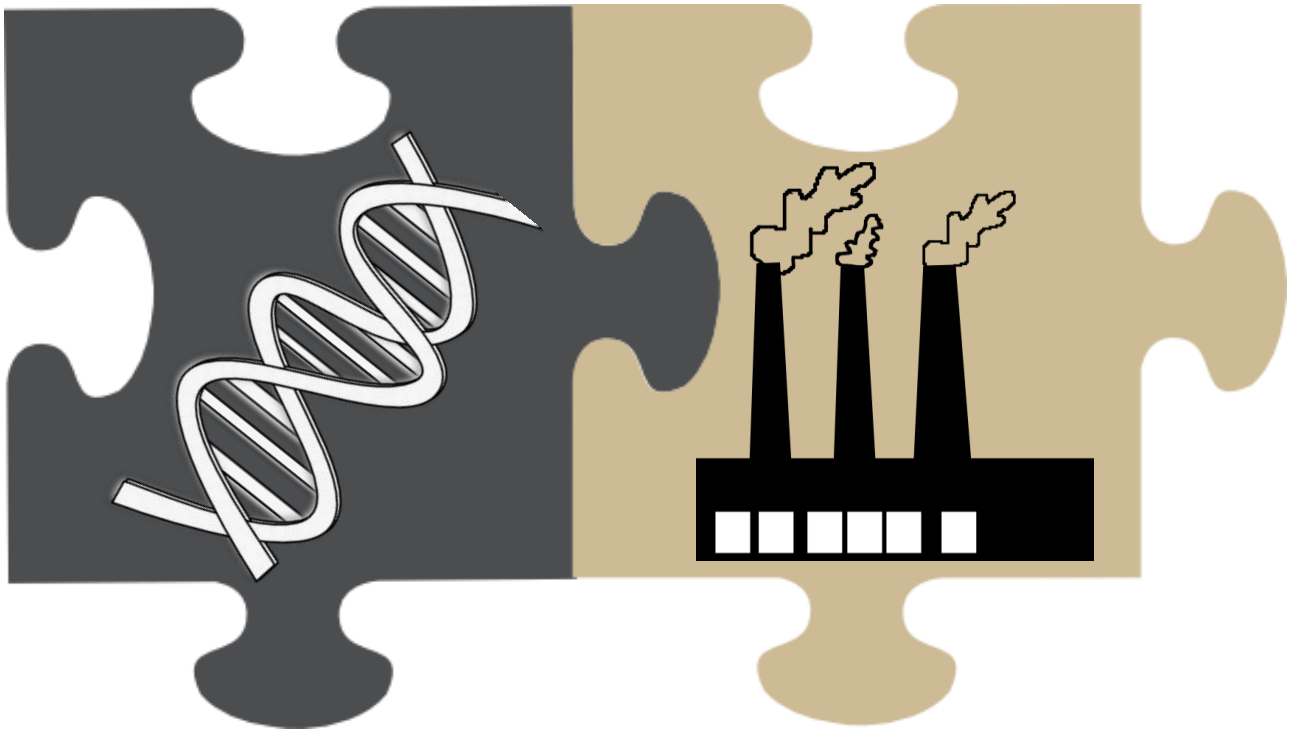
Table 4. Association between Indigenous American ancestry and demographic variables and reproductive risk factors for breast cancer

	% Indigenous American ancestry (*n*)			*P**
	Controls	Cases	All	
Place of birth				
Foreign born	42.6 (200)	42.6 (106)	42.6	0.24
U.S. born	40.1 (129)	40.8 (128)	40.4	
Education				
Some high school or less	45.3 (169)	45.9 (80)	45.5	0.001
High school graduation	40.9 (57)	38.0 (49)	39.6	
Some college	35.7 (53)	37.7 (70)	36.8	
College graduation or higher	36.2 (50)	44.5 (35)	39.6	
Full-term pregnancies				
>2	43.3 (209)	43.7 (124)	43.5	0.01
≤2	38.6 (120)	39.2 (110)	38.9	
Age at first full-term pregnancy				
<30	42.3 (269)	42.7 (173)	41.9	0.50
≥30	41.4 (60)	38.6 (61)	40.4	
Age at menarche				
>12	42.0 (179)	41.3 (101)	41.7	0.89
≥12	41.1 (150)	41.8 (133)	41.5	
BMI				
<25	34.5 (47)	33.2 (48)	33.8	0.0005
25-29.9	45.7 (121)	44.3 (71)	45.2	
30-35	41.7 (86)	42.6 (59)	42.1	
>35	39.3 (75)	44.3 (56)	41.4	
History of hormone therapy use				
Yes	39.4 (124)	37.9 (103)	38.7	0.01
No	42.9 (201)	44.4 (126)	43.5	
Age at menopause†				
<50	45.3 (99)	39.1 (65)	42.8	0.15
≥50	38.3 (55)	39.0 (46)	38.7	

*Ps reported are the significance levels for association between ancestry and the risk factor, using ANOVA and adjusting for case/control status. There were no significant interaction terms among case/control status, genetic ancestry, and any of these risk factors.
† Age at natural or surgical menopause.

- Latinas from Northern California;
- Cases and controls (n=563);
- *Some breast cancer risk factors are associated with ancestry.*

Ziv *et al.* (2006) CEBP 15(10):1878



Global ancestry and breast cancer

- Latinas from Northern California;
- Case (n=492) and controls (n=670);
- *European ancestry was associated with breast cancer risk.*

Table 2. Multivariate logistic regression model of association between genetic ancestry and breast cancer risk (n = 975)

	OR (95% CI)	$P > \|z\|$
Univariate analysis		
European ancestry*	1.79 (1.28–2.79)	<0.001
Multivariate analysis		
European ancestry	1.39 (1.06–2.11)	0.013
Age at diagnosis	1.02 (1.01–1.04)	0.013
Foreign born	0.73 (0.54–0.99)	0.046
Family history of breast cancer	1.34 (0.88–2.04)	0.160
Benign breast disease	1.12 (0.77–1.59)	0.580
Age at menarche	0.93 (0.86–1.01)	0.074
Hormone replacement therapy use	0.92 (0.68–1.24)	0.570
Daily alcohol intake †	1.98 (1.21–3.24)	0.006
Ln daily kilocalorie intake ‡	1.78 (1.24–2.42)	0.001
Parity	0.86 (0.80–0.94)	<0.001
Breast-feeding per child	0.97 (0.95–1.00)	0.070
Education level	1.11 (0.96–1.28)	0.131

NOTE: Thirty-two cases and 25 controls were excluded from the analysis because of missing data.
*OR is for every 25% increase in European ancestry.
†Daily intake of >10 versus ≤10 g.
‡Individuals with daily kilocalorie intake of <600 or >5,000 were excluded from the analysis. Daily kilocalorie intake was log transformed for analysis.

Fejerman *et al*. Cancer Research 2008; 68(23):9723-8

Global ancestry and breast cancer

Research Article

Cancer Epidemiology, Biomarkers & Prevention

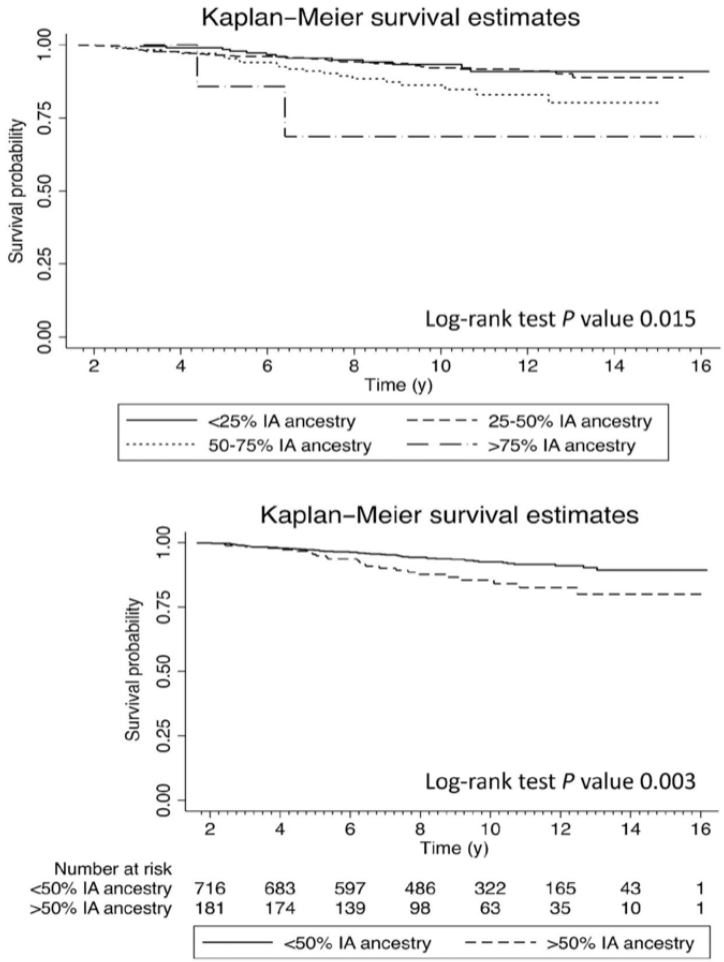
European Ancestry Is Positively Associated with Breast Cancer Risk in Mexican Women

Laura Fejerman[1,3], Isabelle Romieu[6,7], Esther M. John[8,9], Eduardo Lazcano-Ponce[6], Scott Huntsman[1,3], Kenneth B. Beckman[10], Eliseo J. Pérez-Stable[2,3], Esteban González Burchard[5], Elad Ziv[1,3,4], and Gabriela Torres-Mejía[6]

Abstract

The incidence of breast cancer is 35% lower in Hispanic women living in the San Francisco Bay Area than in non-Hispanic White women. We have previously described a significant association between genetic ancestry and risk for breast cancer in a sample of U.S. Hispanics/Latinas. We retested the association in women residing in Mexico because of the possibility that the original finding may be confounded by U.S. specific unmeasured environmental exposures. We genotyped a set of 106 ancestry informative markers in 846 Mexican women with breast cancer and 1,035 unaffected controls and estimated genetic ancestry using a maximum likelihood method. Odds ratios and 95% confidence intervals (95% CI) for ancestry modeled as a categorical and continuous variable were estimated using logistic regression and adjusted for reproductive and other known risk factors. Greater European ancestry was associated with increased breast cancer risk in this new and independent sample of Mexican women residing in Mexico. Compared with women with 0% to 25% European ancestry, the risk was increased for women with 51% to 75% and 76% to 100% European ancestry [odds ratios, 1.35 (95% CI, 0.96-1.91) and 2.44 (95% CI, 0.94-6.35), respectively; P for trend = 0.044]. For every 25% increase in European ancestry (modeled as a continuous variable), there was a 20% increase in risk for breast cancer (95% CI, 1.03-1.41; $P = 0.019$). These results suggest that nongenetic factors play a crucial role in explaining the difference in breast cancer incidence between Latinas and non-Latina White women, and it also points out to the possibility of a genetic component to this difference. *Cancer Epidemiol Biomarkers Prev; 19(4); 1074–82. ©2010 AACR.*

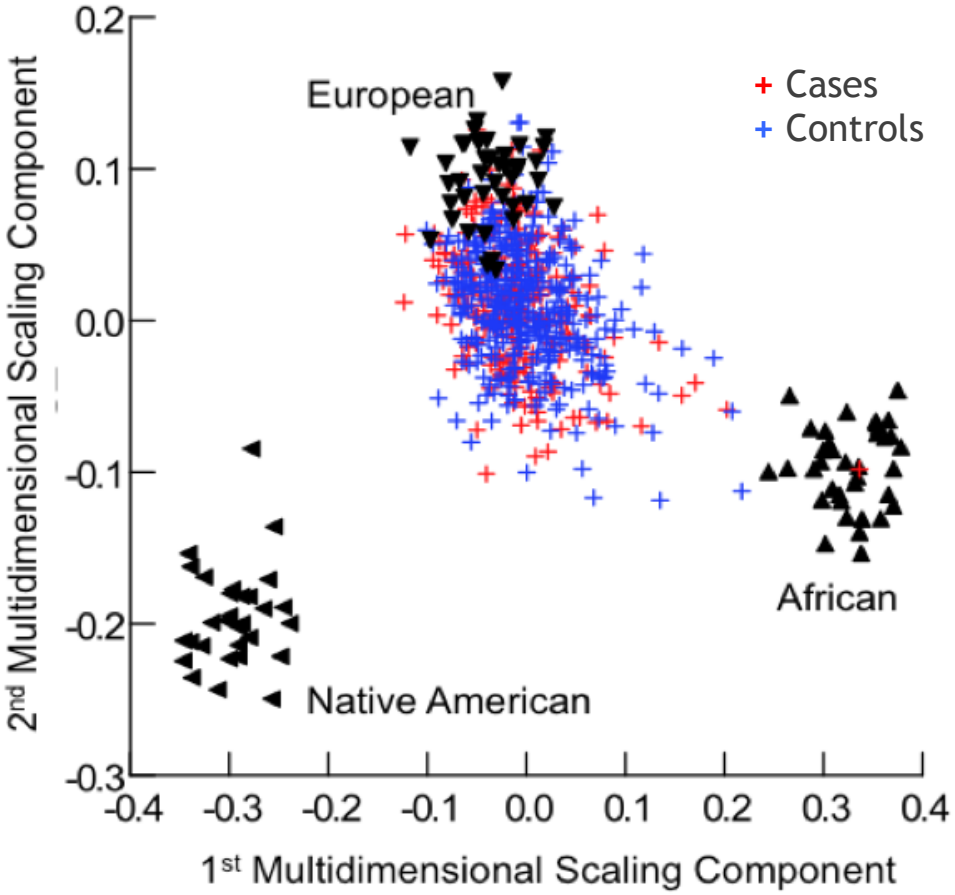
Global ancestry and breast cancer



- Latinas from Northern California;
- Cases (n=899);
- *Women with higher Indigenous American ancestry were more likely to die of breast cancer.*

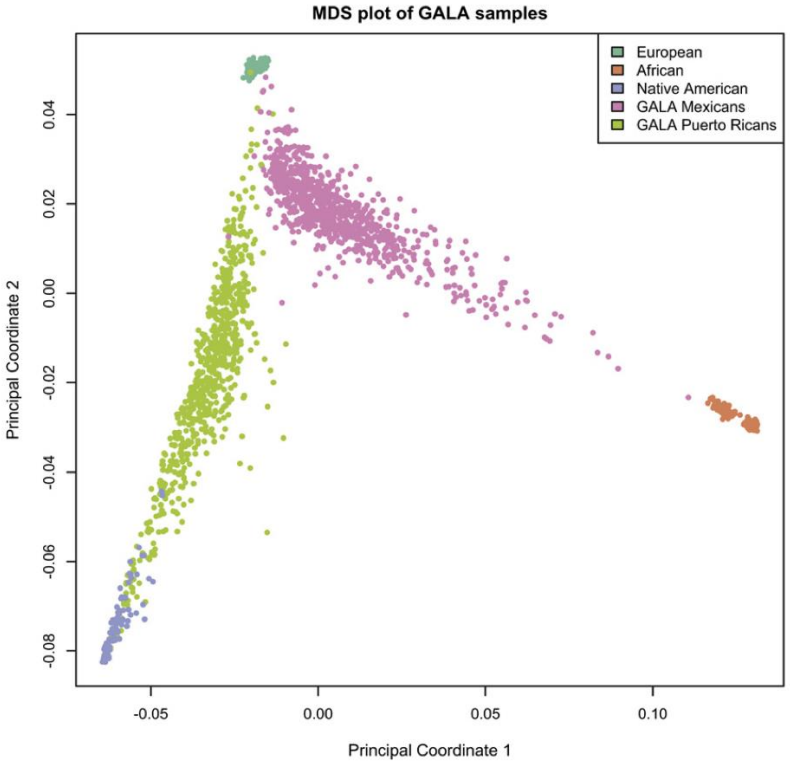
Fejerman *et al.* (2013) Cancer Research 73(24):7243

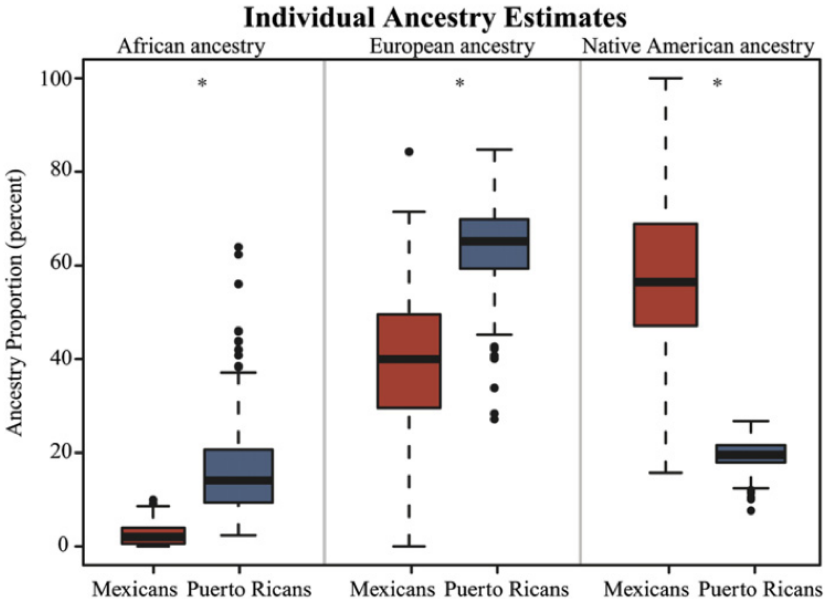
Global ancestry and breast cancer



- Hispanics from Puerto Rico;
- Cases (n=500) and controls (n=500)
- *Ancestry is not associated with breast cancer risk.*

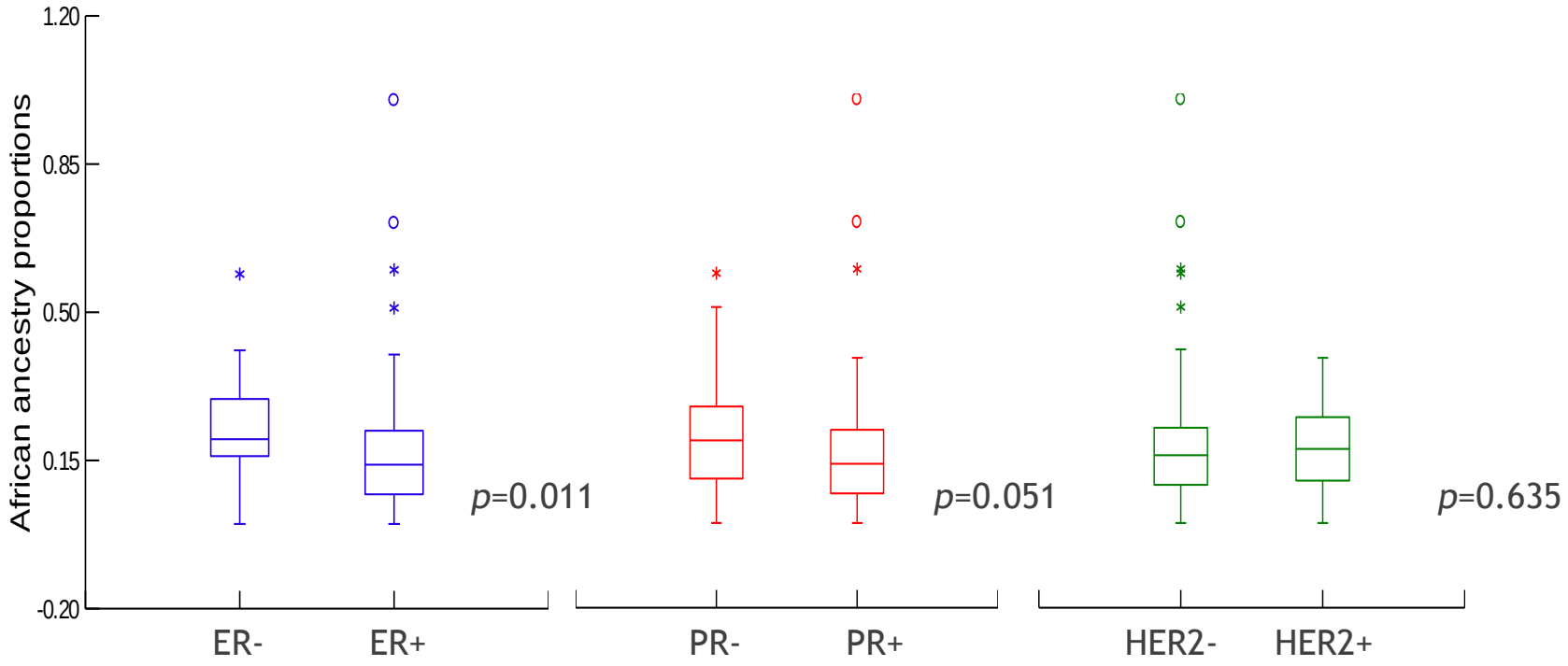
Dutil et al. manuscript submitted





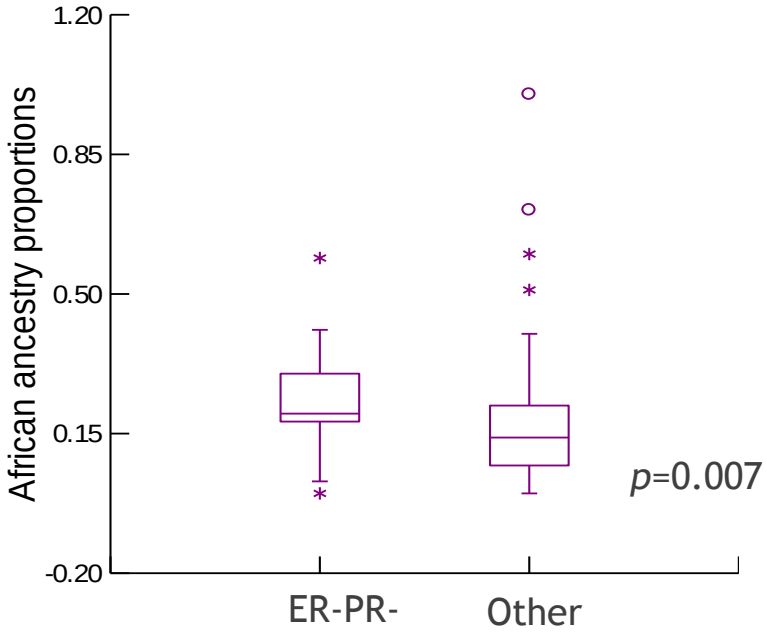
Galanter *et al*. (2011) J Allergy Clin Immunol 128(1):37

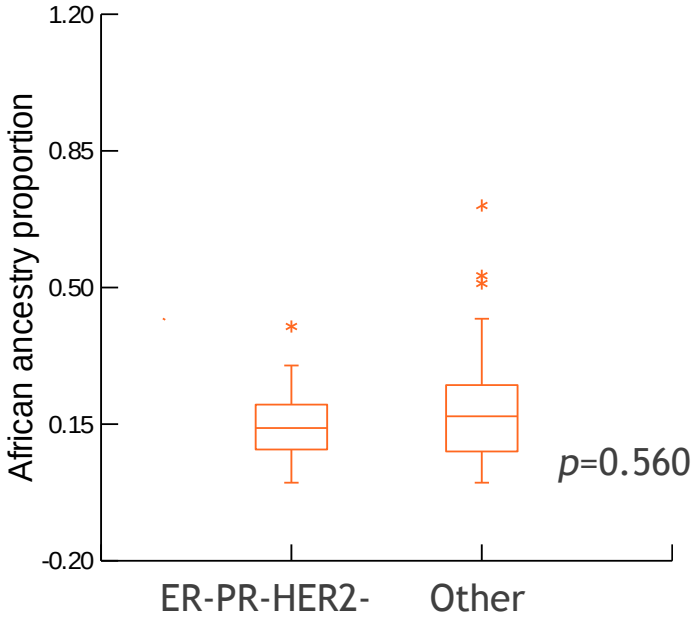
Global ancestry and breast cancer



Dutil *et al*. manuscript submitted

Global ancestry and breast cancer





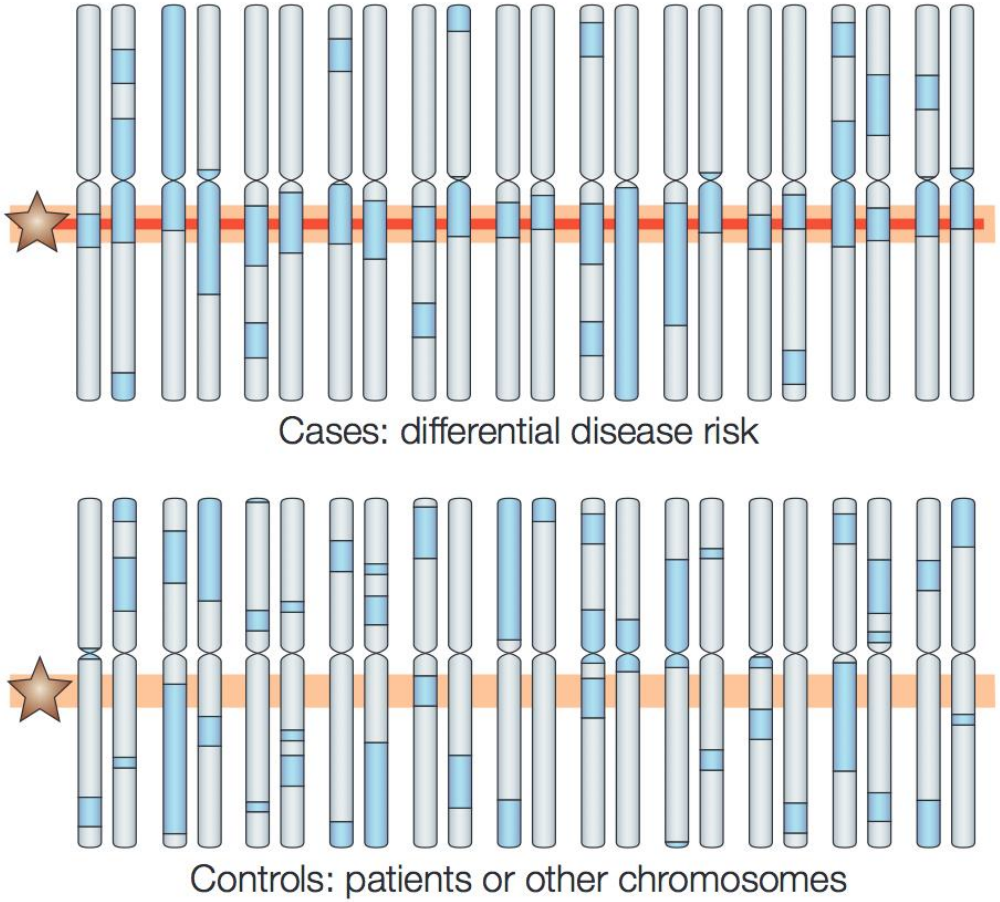
Dutil *et al*. manuscript submitted

Admixture mapping

- Genetic association strategy that make use of admixture for identifying disease susceptibility loci;

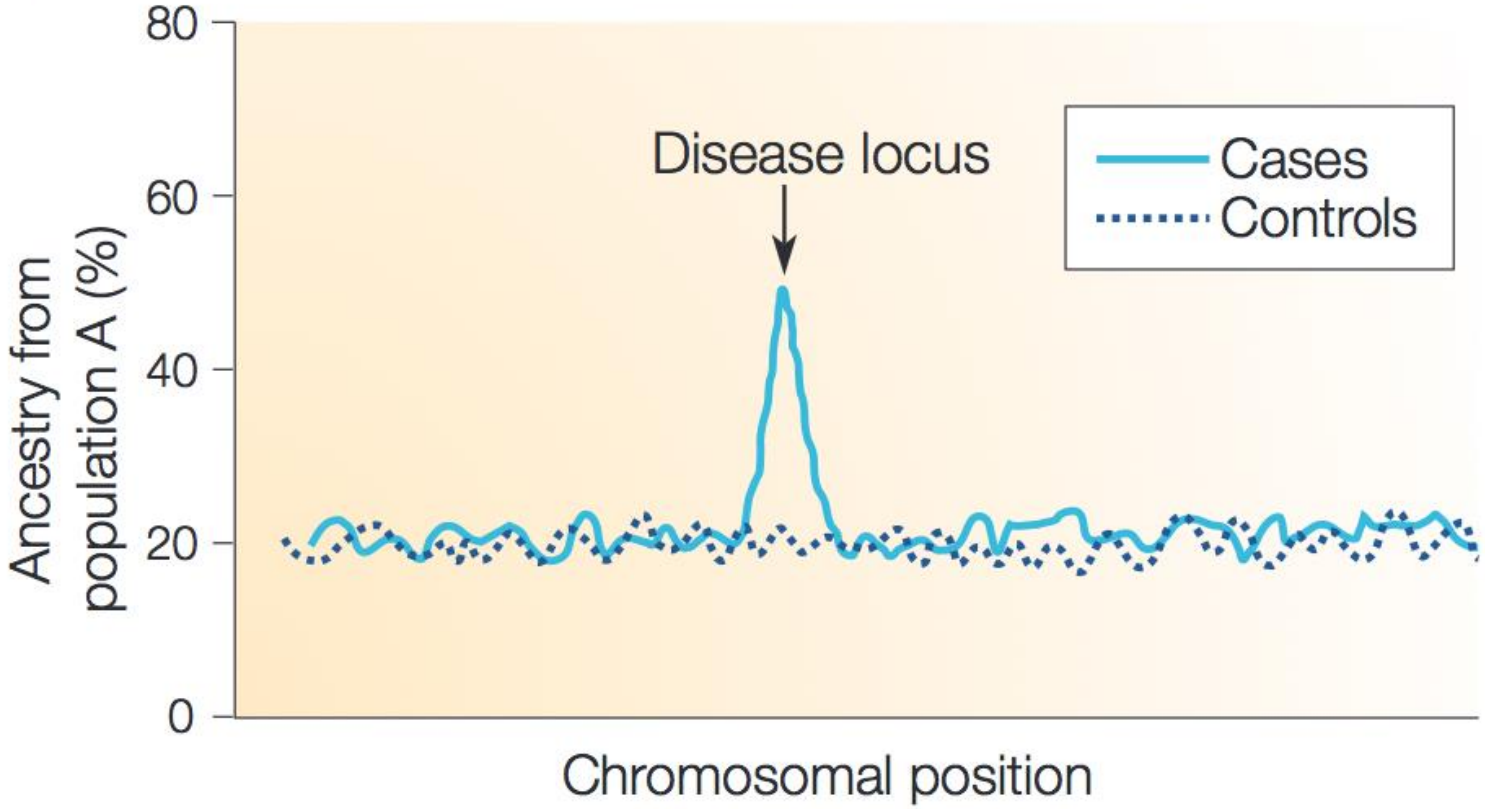
- Suitable for localizing disease causing alleles that have marked difference of frequency between the different ancestral populations that formed the admixed population.

Admixture mapping



Smith *et al.* Nature Reviews Genetics (2005) 6:623

Admixture mapping



Smith *et al.* Nature Reviews Genetics (2005) 6:623

Admixture mapping

- Advantages:
  - Sample size;
  - Number of markers/cost;
  - Understanding health disparities

- Limitations:
  - Must have marked differences in disease prevalence;
  - Does not identify all disease causing variants.

Admixture mapping

- Use of admixture mapping for identifying breast cancer susceptibility loci;

- Use of admixture mapping for the identification of prostate cancer susceptibility loci.

Breast cancer admixture mapping

Human Molecular Genetics, 2012, Vol. 21, No. 8 **1907–1917**
doi:10.1093/hmg/ddr617
Advance Access published on January 6, 2012

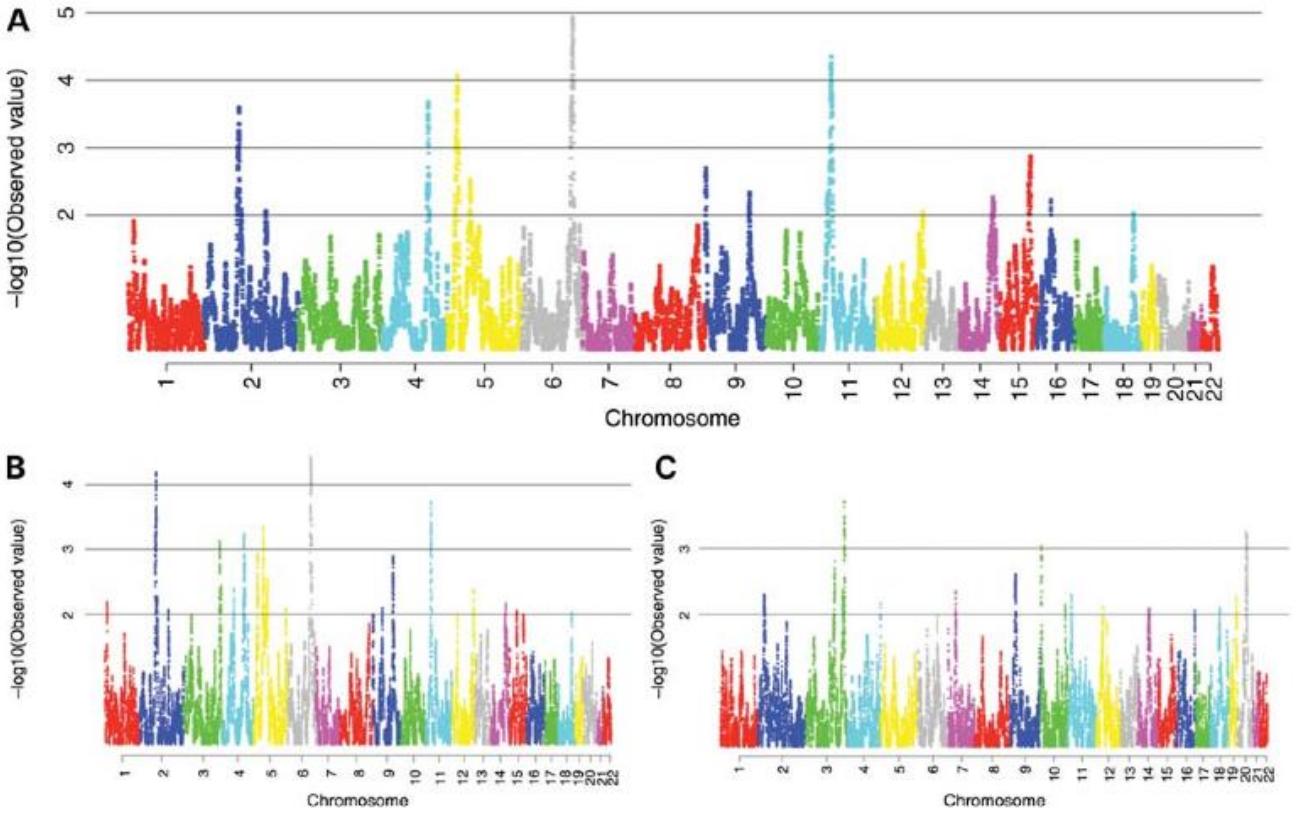
Admixture mapping identifies a locus on 6q25 associated with breast cancer risk in US Latinas

Laura Fejerman[1], Gary K. Chen[3], Celeste Eng[2], Scott Huntsman[1], Donglei Hu[1], Amy Williams[4], Bogdan Pasaniuc[5], Esther M. John[6,7], Marc Via[2,10], Christopher Gignoux[2], Sue Ingles[3], Kristine R. Monroe[3], Laurence N. Kolonel[8], Gabriela Torres-Mejía[9], Eliseo J. Pérez-Stable[1], Esteban González Burchard[2], Brian E. Henderson[3], Christopher A. Haiman[3,*] and Elad Ziv[1,*]

[1]Department of Medicine, Division of General Internal Medicine, Institute for Human Genetics and Helen Diller Family Comprehensive Cancer Center and [2]Department of Medicine, Pulmonary and Critical Care Division, Institute for Human Genetics, University of California San Francisco, San Francisco, CA 94158, USA, [3]Department of Preventive Medicine, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA, [4]Department of Genetics, Harvard Medical School, Boston, MA 02115, USA, [5]Dept of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA and [6]Cancer Prevention Institute of California, Fremont, CA 94538, USA, [7]Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA 94305, USA, [8]University of Hawaii Cancer Center, Honolulu, HI 96813, USA, [9]Instituto Nacional de Salud Publica, Cuernavaca, Morelos 62100, Mexico, and [10]Unit of Anthropology, Department of Animal Biology, Universitat de Barcelona, Barcelona, Spain

Received August 10, 2011; Revised October 23, 2011; Accepted December 28, 2011

Breast cancer admixture mapping



Fejerman *et al.* 2012 Human Molecular Genetics 21(8):1907-1917

Breast cancer admixture mapping

ARTICLE

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Genome-wide association study of breast cancer in Latinas identifies novel protective variants on 6q25

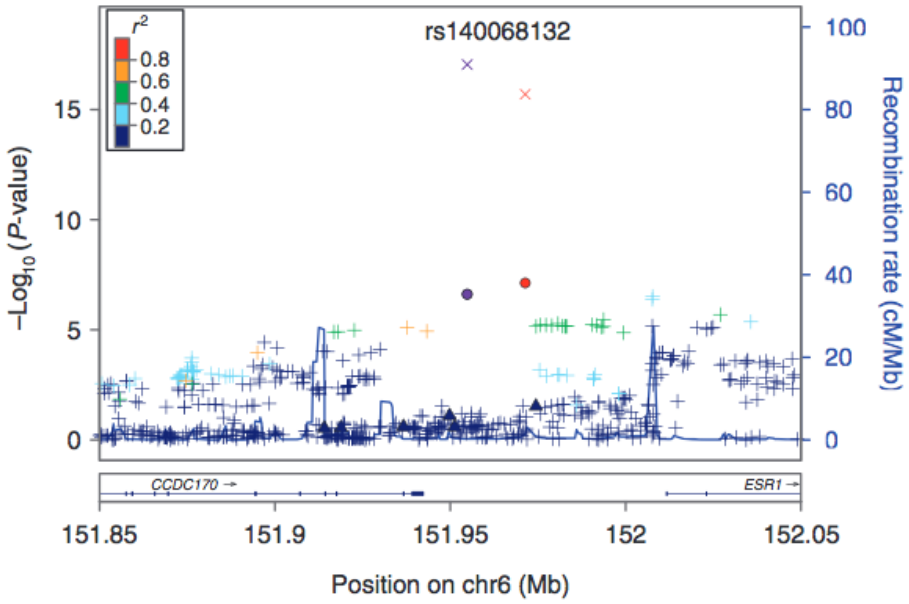
Laura Fejerman[1], Nasim Ahmadiyeh[2], Donglei Hu[1], Scott Huntsman[1], Kenneth B. Beckman[3], Jennifer L. Caswell[1], Karen Tsung[2], Esther M. John[4,5], Gabriela Torres-Mejia[6], Luis Carvajal-Carmona[7,8], María Magdalena Echeverry[7], Anna Marie D. Tuazon[7], Carolina Ramirez[8], COLUMBUS Consortium[†], Christopher R. Gignoux[9], Celeste Eng[10], Esteban Gonzalez-Burchard[10], Brian Henderson[11], Loic Le Marchand[12], Charles Kooperberg[13], Lifang Hou[14], Ilir Agalliu[15], Peter Kraft[16], Sara Lindström[16], Eliseo J. Perez-Stable[1], Christopher A. Haiman[11] & Elad Ziv[1]

Breast cancer admixture mapping

Table 1 | Discovery and replication of newly discovered protective variants at 6q25 related to breast cancer risk in Latinas.

6q25 Region	Alleles*	OR	95% CI	P value	MAF†
Discovery (1,497 cases/3,213 controls)					
rs140068132	A/G	0.60	0.49–0.72	3×10^{-7}	9%
rs147157845	C/A	0.59	0.48–0.72	1×10^{-7}	9%
Replication Mexicans (977 cases/1,158 controls)					
rs140068132		0.63	0.53–0.75	3×10^{-7}	15%
rs147157845		0.66	0.55–0.78	3×10^{-6}	15%
Replication Colombians (546 cases/440 controls)					
rs140068132		0.54	0.41–0.71	1×10^{-5}	10%
rs147157845		0.55	0.42–0.72	2×10^{-5}	10%
Replication WHI Hispanics (120 cases/3,373 controls)					
rs140068132		0.61	0.31–1.22	0.16	7%
rs147157845		0.60	0.30–1.19	0.15	7%
Meta-analysis (3,140 cases/8,184 controls)					
rs140068132		0.60	0.53–0.67	9×10^{-18}	
rs147157845		0.61	0.54–0.68	2×10^{-16}	

CI, confidence interval; MAF, minor allele frequency; OR, odds ratio; WHI, Women's Health Initiative.
*Reference allele/tested allele.
†MAF: tested allele.



Fejerman *et al.* (2014) Nature Communications 5:5261

Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men

Matthew L. Freedman[a,b,c], Christopher A. Haiman[c,d], Nick Patterson[b,c], Gavin J. McDonald[b,e], Arti Tandon[b,e], Alicja Waliszewska[b,e,f], Kathryn Penney[b], Robert G. Steen[e,g], Kristin Ardlie[b,h], Esther M. John[i,j], Ingrid Oakley-Girvan[i,j], Alice S. Whittemore[j], Kathleen A. Cooney[k,l], Sue A. Ingles[d], David Altshuler[b,e,m,n], Brian E. Henderson[d], and David Reich[b,e,o]

[a]Department of Medical Oncology, Dana–Farber Cancer Institute, Boston, MA 02115; [b]Prog
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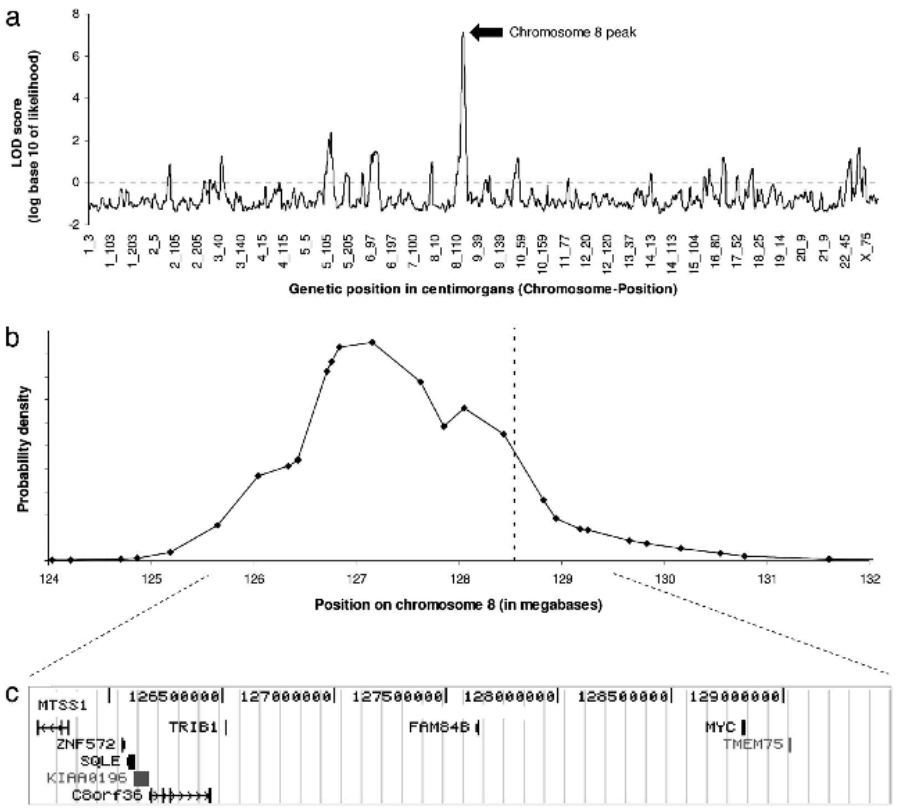
Stanford University School of Medicine, Stanford, CA 94305; [k]Departments of Medicine and
Michigan, Ann Arbor, MI 48109; and [n]Center for Human Genetic Research and Department
Boston, MA 02114

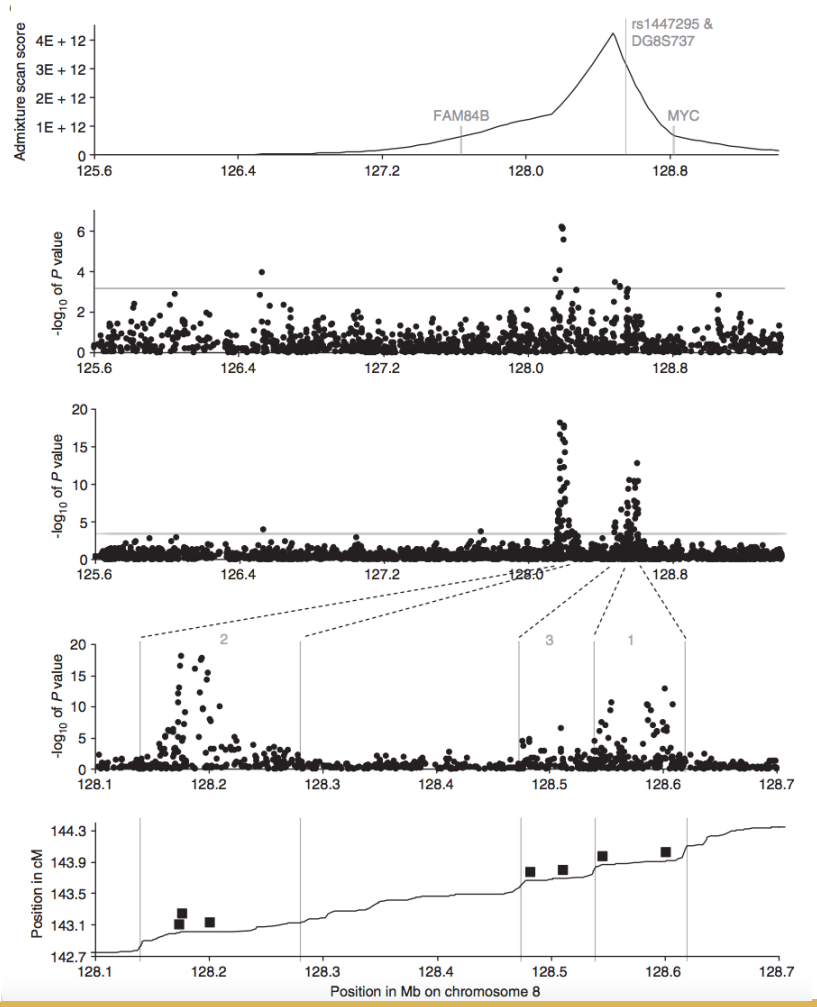
Communicated by Eric S. Lander, Broad Institute, Cambridge, MA, July 12, 2006 (received fo



Freedman *et al.* (2006) PNAS 103(38): 14068

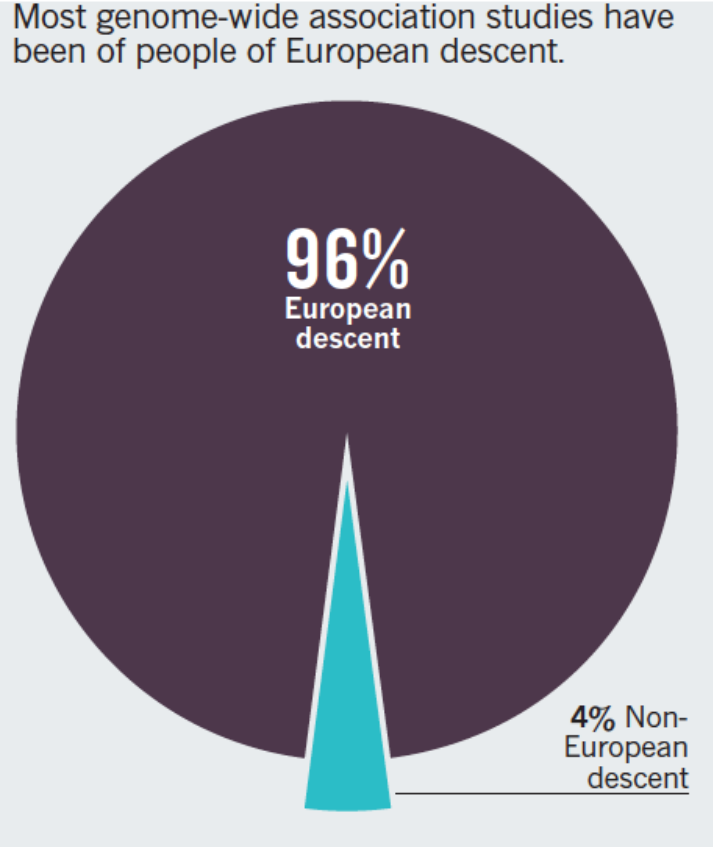
Multiple regions within 8q24 independently affect risk for prostate cancer

Christopher A Haiman[1], Nick Patterson[2], Matthew L Freedm
Alicja Waliszewska[2,4,5], Julie Neubauer[2,4], Arti Tandon[2,4], Chr
Steven C Greenway[4], Daniel O Stram[1], Loic Le Marchand[6], I
David Wong[1], Loreall C Pooler[1], Kristin Ardlie[2,7], Ingrid Oak
Kathleen A Cooney[10,11], Esther M John[8,9], Sue A Ingles[1], Dav
Brian E Henderson[1] & David Reich[2,4]



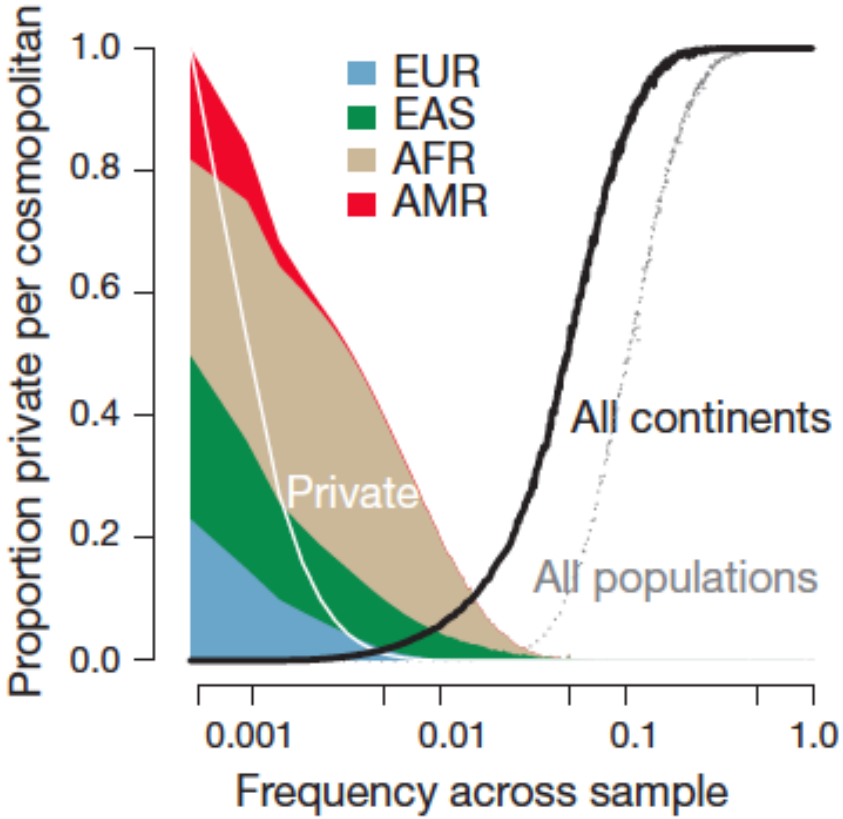
Hainan *et al.* (2007) Nature Genetics 39(5): 638

Sampling bias in genomics



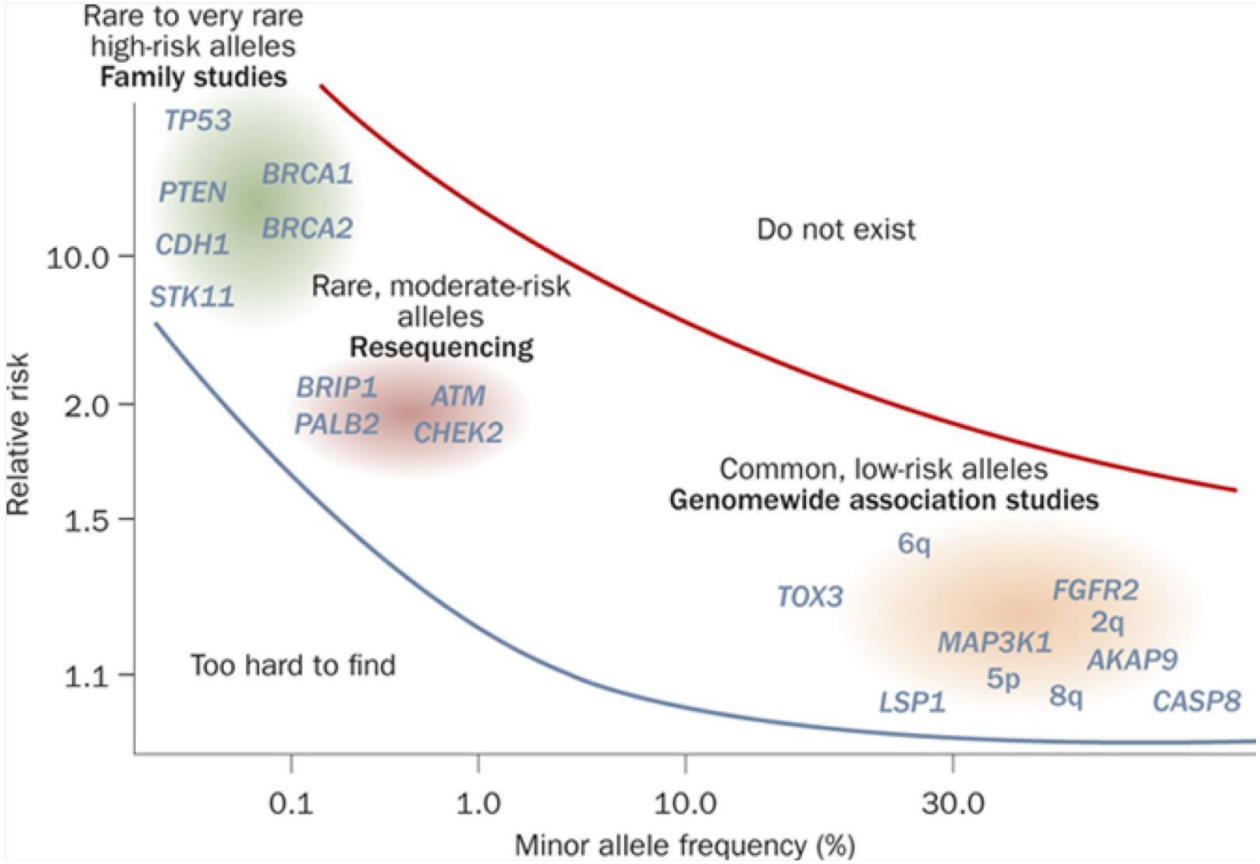
Bustamante CD, Gonzalez Burchard E, De La Vega FM (2011) Nature 475:163

Private and shared variants



The 1000 Genomes Project Consortium. (2012) Nature 491: 56

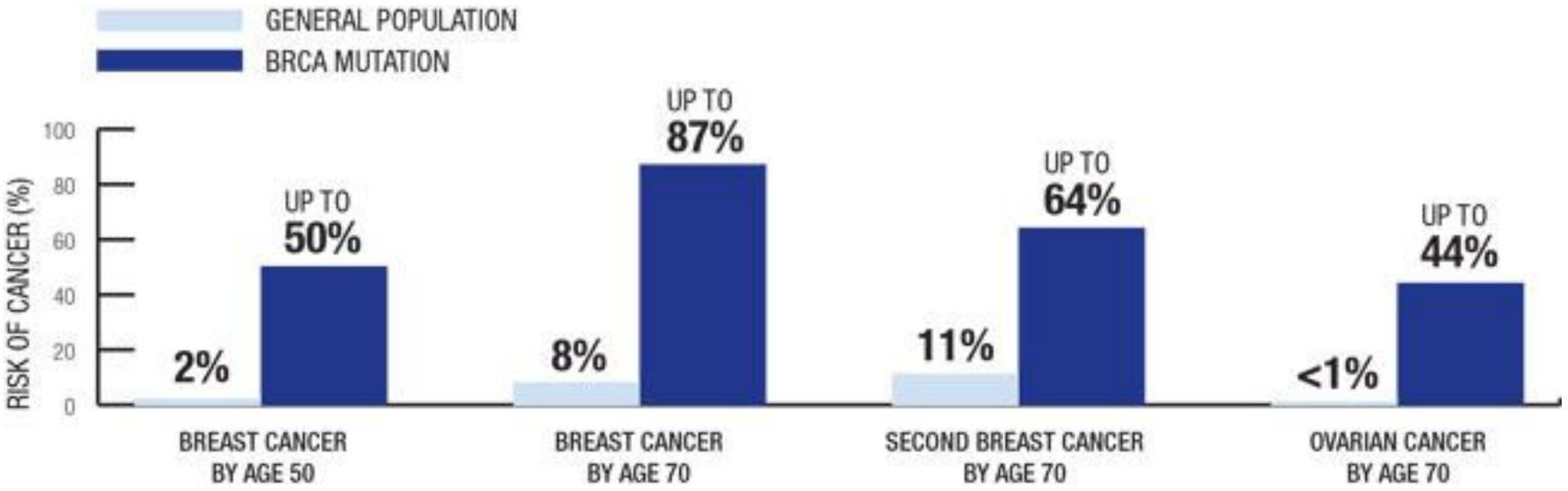
Cancer genetics



Timothy J. R. Harris & Frank McCormick
Nature Reviews Clinical Oncology 7, 251-265 (May 2010)

BRCA clinical significance

Cancer risks in BRCA carriers relative to the general population.



Myriad Genetics Laboratories

BRCA mutation spectrum

Literature search
PubMed MeSH search, Google Scholar, literature cited

↓

Standardization of the mutations to BIC nomenclature

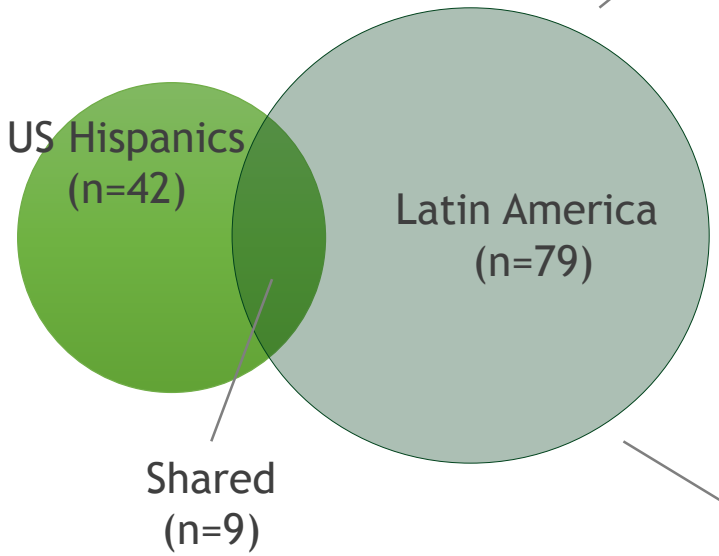
↓

Compiled mutations prevalence, spectrum and recurrence for each country of Latin America, the Caribbean, and US Hispanics/Latinos populations

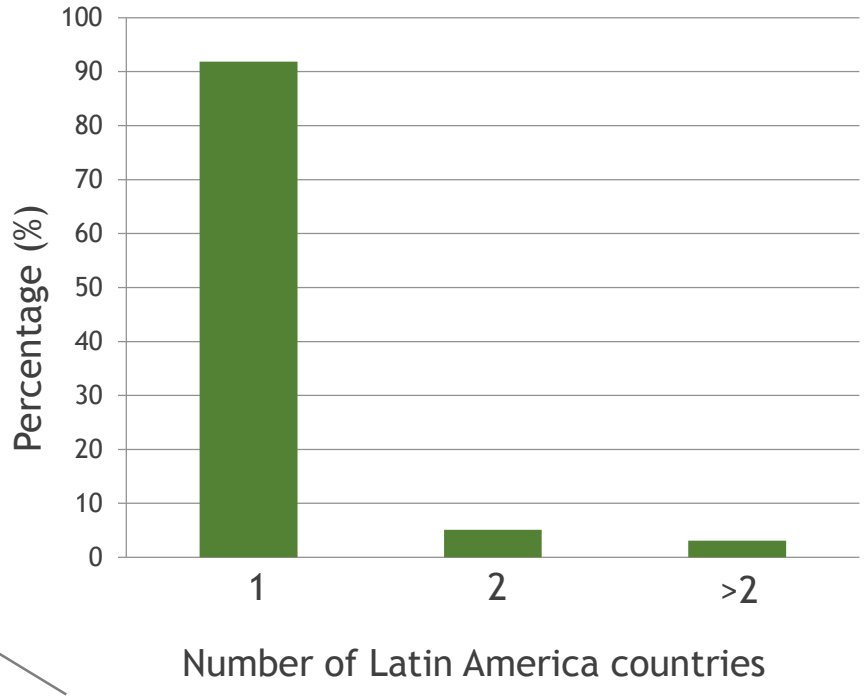
Dutil *et al*. Manuscript submitted

BRCA mutation spectrum

Proportions of shared BRCA1/2 mutations between US Hispanics and Latin America



Proportion of *BRCA1/2* mutations shared among Latin America populations



Dutil *et al*. Manuscript submitted

Conclusions

- Genetic ancestry and environmental factors explain some of the differences in disease risk and presentation among different ethnic groups;
- Admixture mapping have been used for localizing regions of the genome or variants underlying the inter-ethnic differences in cancer susceptibility (breast and prostate);
- A better understanding of the genetic basis to cancer susceptibility is a key component for eliminating cancer health disparity.

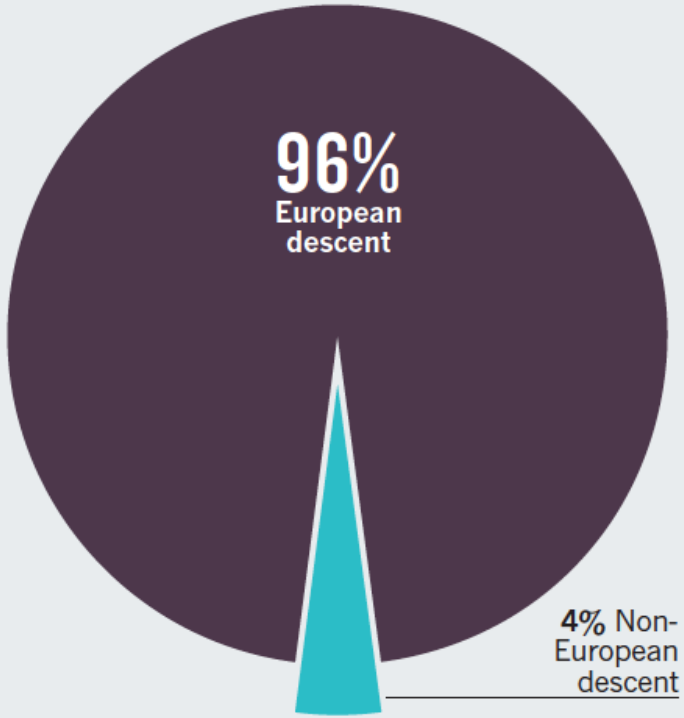
Conclusions

CLOCKWISE FROM TOP LEFT: O. STREW/© LONELY PLANET IMAGES; A. DISANAYAKE/ LONELY PLANET IMAGES; K. COOLE/ LONELY PLANET IMAGES; K. OKUVOVA/ AP IMAGES; T. VOETEV PANOS; R. IANSON/ LONELY PLANET IMAGES; J. HAGLUND/ LONELY PLANET IMAGES; P. ADAMS/ GETTY IMAGES

Genomics for the world

SAMPLING BIAS

Most genome-wide association studies have been of people of European descent.



Bustamante CD, Gonzalez Burchard E, De La Vega FM (2011) Nature 475:163