Why should we consider engagement of diverse communities in genetics and genomics research:

Camille Ragin, PhD, MPH
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FOX CHASE CANCER CENTER
TEMPLE HEALTH

Outline

- **Lecture #1: Health Disparities and Genetics**
  - Overview of Health Disparities
  - Genetics 101 – Introduction Genetic Diversity
  - How the Environment and Behavior Influence Genetic Effects on Disease
- **Lecture #2: Genetic Diversity Effects on Disease**
  - Overview of Genetic Diversity and Genetic Ancestry
  - Examples of How Genetic Diversity/Ancestry Influence The Biology of a Disease as well as Outcomes from Disease
  - Why Engagement of Diverse Communities in Genetics and Genomics Research Matters

Lecture #1
Health Disparities and Genetics

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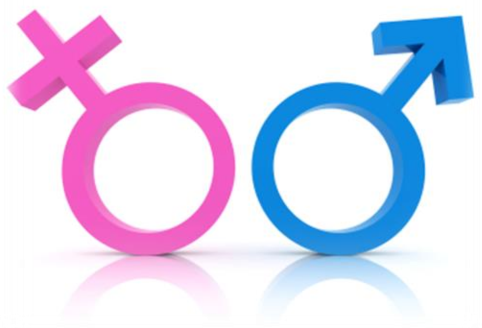
Disparity

- Definition:

"Health Disparities are differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups in the United States" ***(NIH)***

Types of Health Disparities

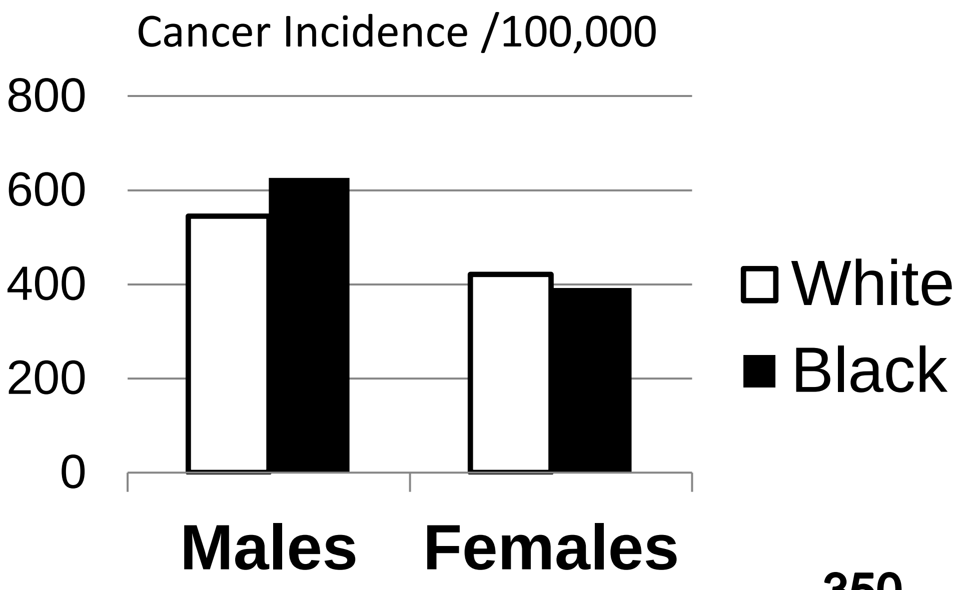
- Gender

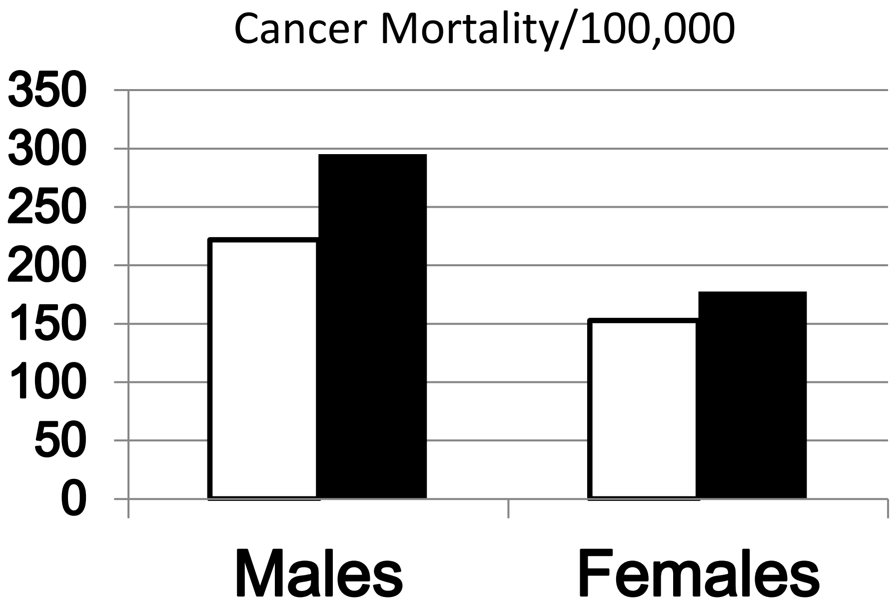


- Race/Ethnicity

- Geography

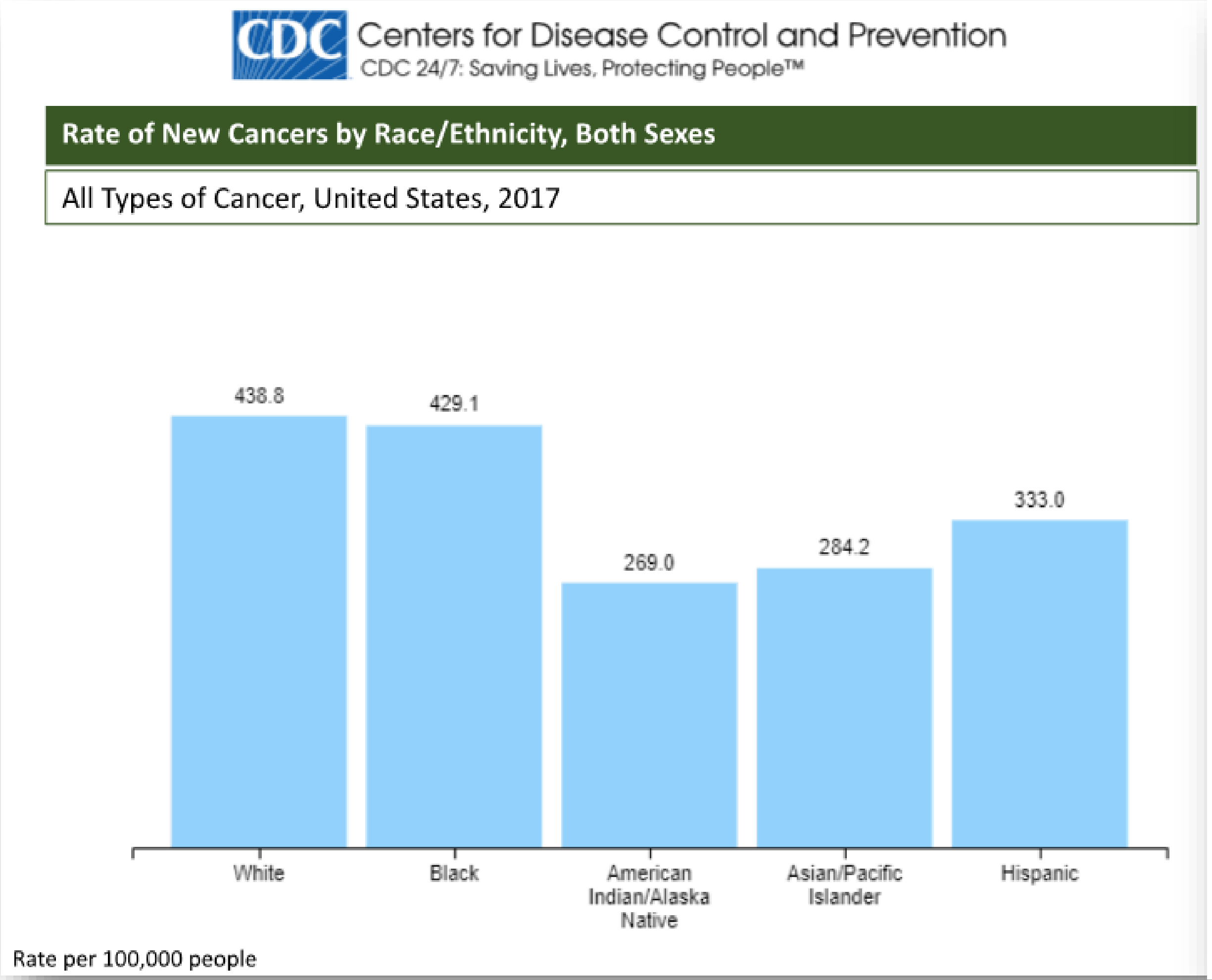
Gender Disparities - Example

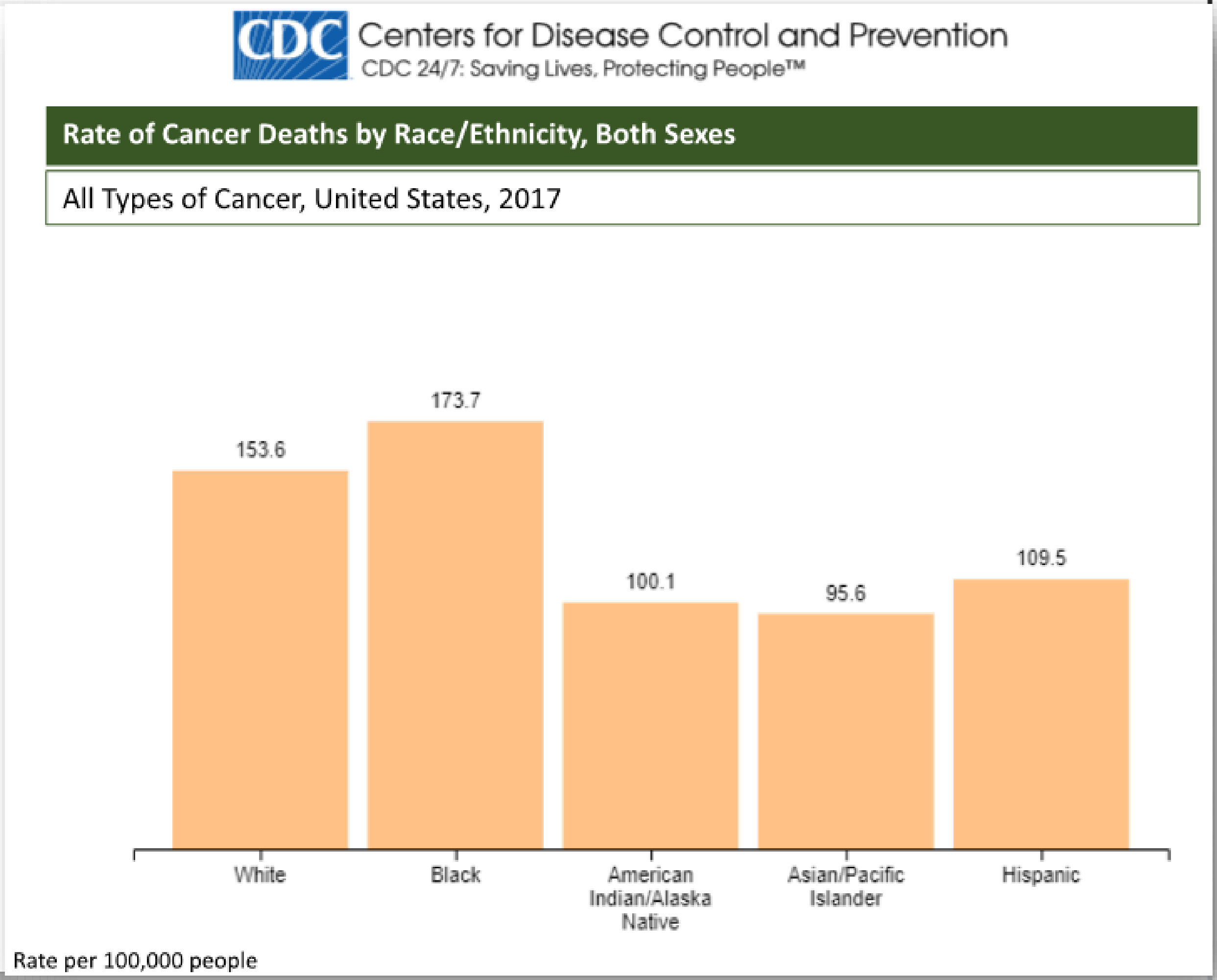




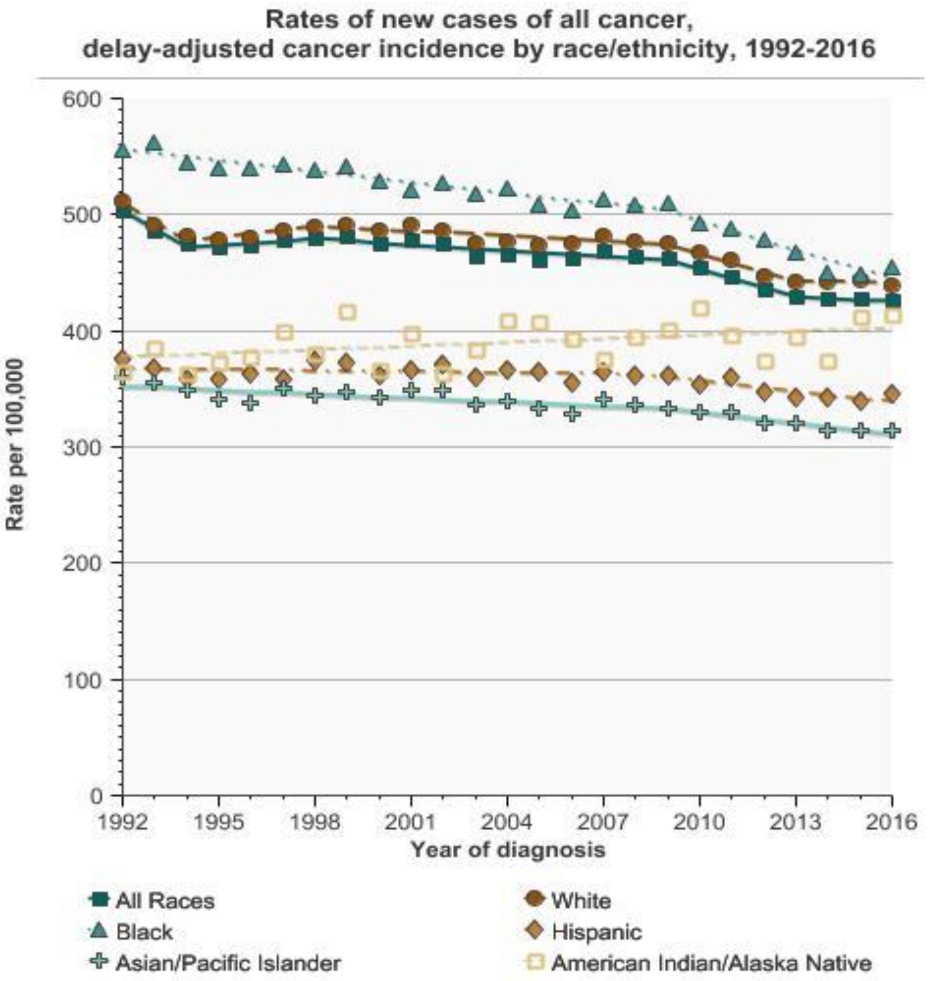
CA CANCER J CLIN 2012;62:10–29

Racial Disparities – Example 1

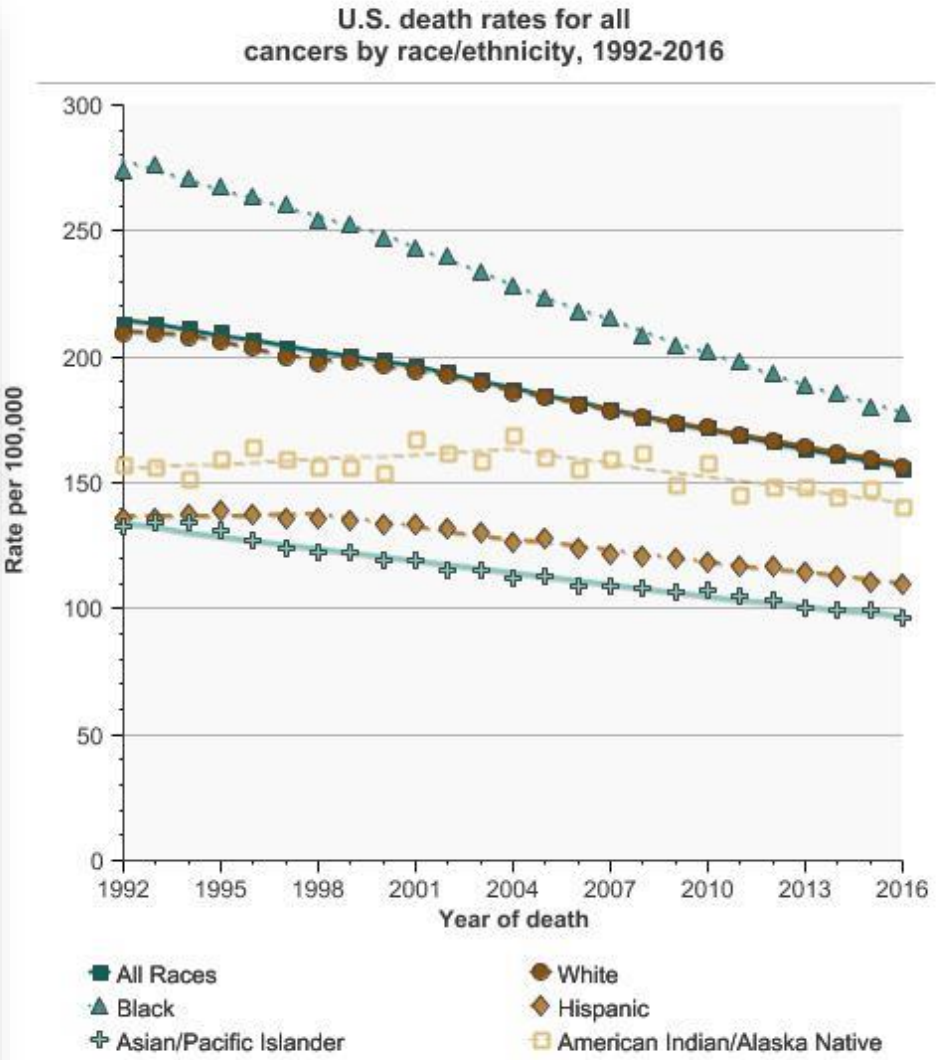




Racial Disparities – Example 2



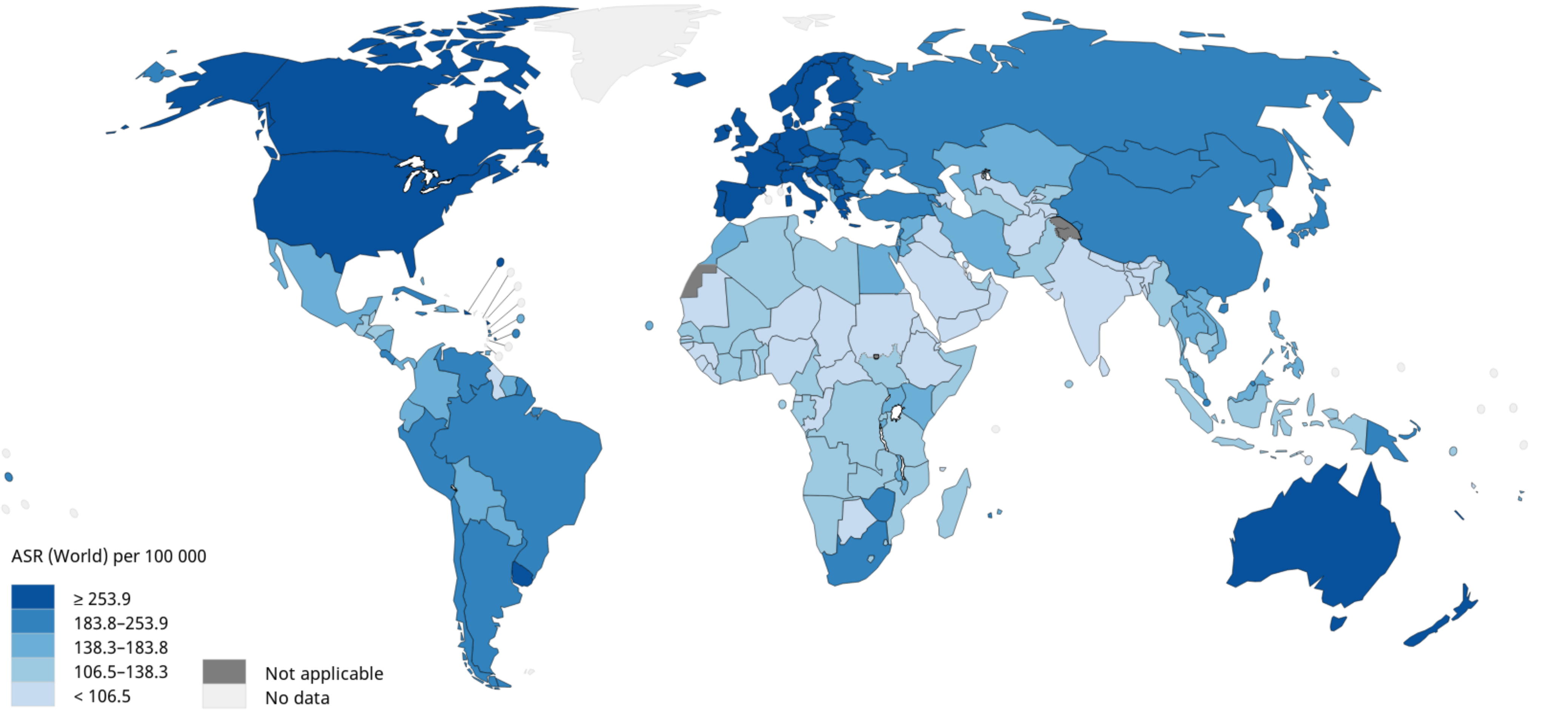
Source: SEER Program, National Cancer Institute. Incidence data are from the SEER 13 areas (http://seer.cancer.gov/registries/terms.html).
Data are age-adjusted to the 2000 US standard population using age groups: <1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85+.



Source: National Center for Health Statistics data as analyzed by NCI.
Data are age-adjusted to the 2000 US standard population using age groups: <1, 1-4, 5-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, 85+.

Geographic Disparities – Example 1

Estimated age-standardized incidence rates (World) in 2018, all cancers, both sexes, all ages

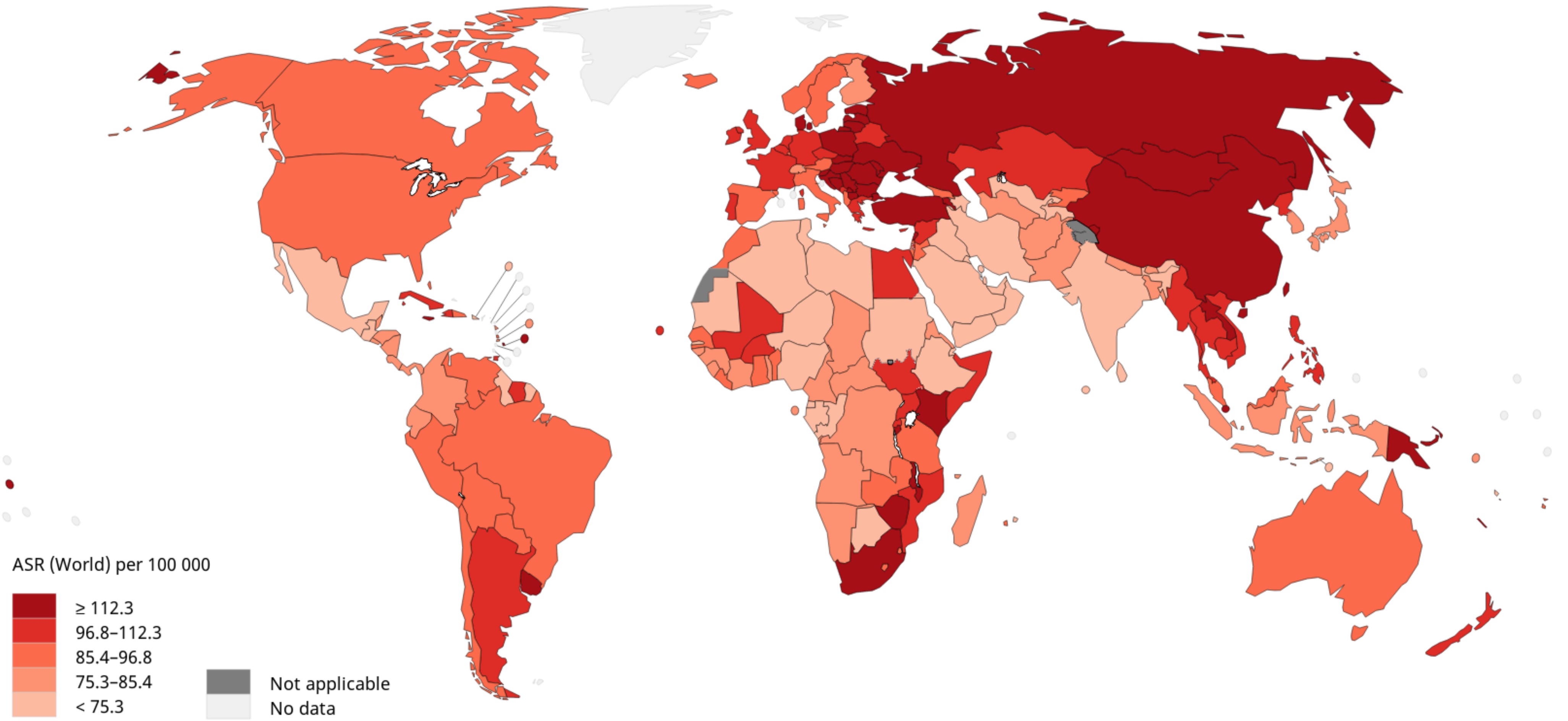


Data source: GLOBOCAN 2018
Graph production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization

Geographic Disparities – Example 2

Estimated age-standardized mortality rates (World) in 2018, all cancers, both sexes, all ages



Data source: GLOBOCAN 2018
Graph production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization

Leading Causes of Death, U.S.

Disparities exist as countries transition at rates of epidemiologic transition

1900

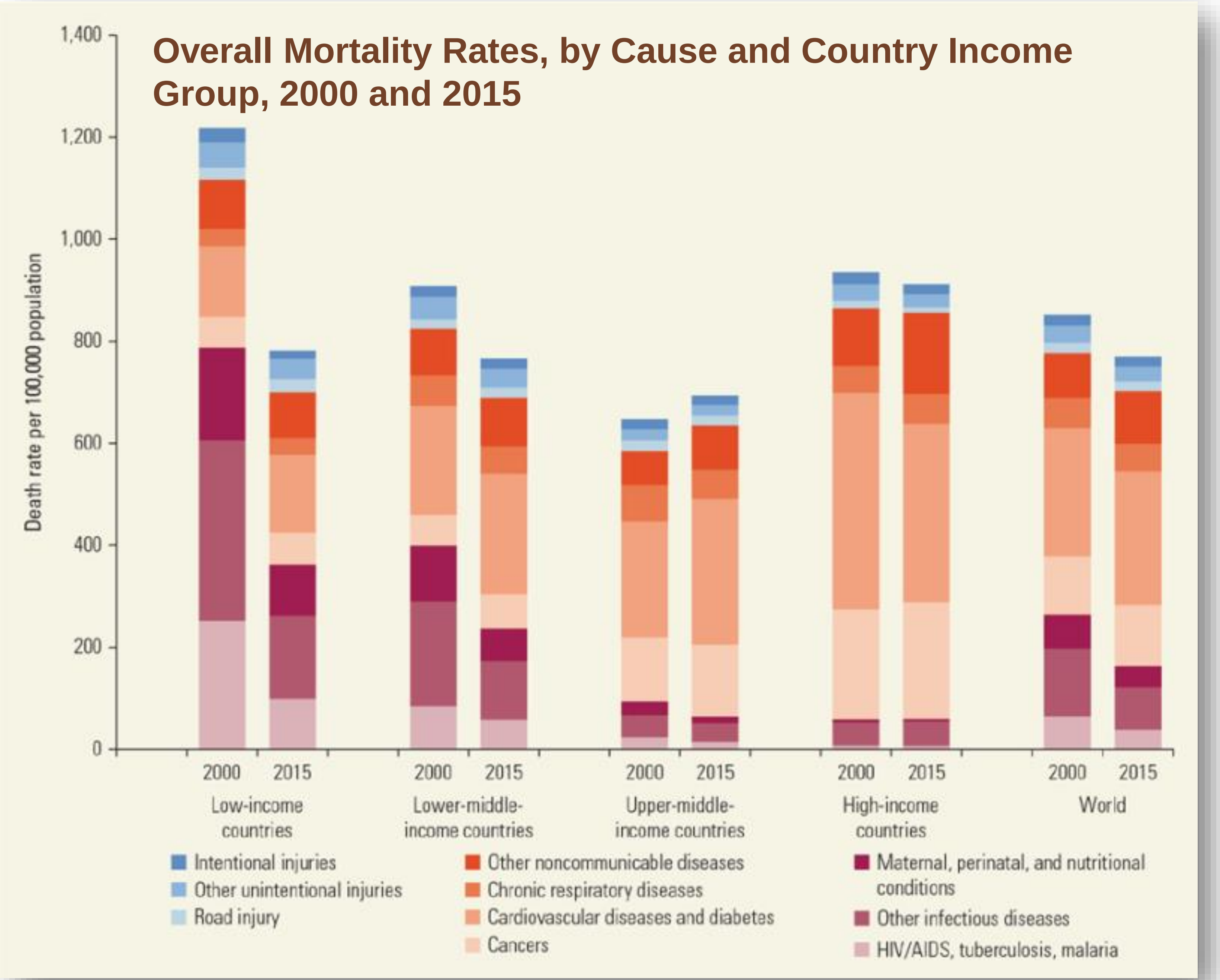
1. Influenza & Pneumonia
2. Tuberculosis
3. Heart Disease
4. Stroke
5. Diarrhea/Enteritis
6. Nephritis
7. Cancer
8. Accidents (unintentional Injuries)
9. Diphtheria
10. Diseases of Early Infancy

2000

1. Heart Disease
2. Cancer
3. Stroke
4. COPD
5. Accidents (unintentional injuries)
6. Diabetes
7. Influenza & Pneum.
8. Alzheimer's Disease
9. Nephritis
10. Septicemia

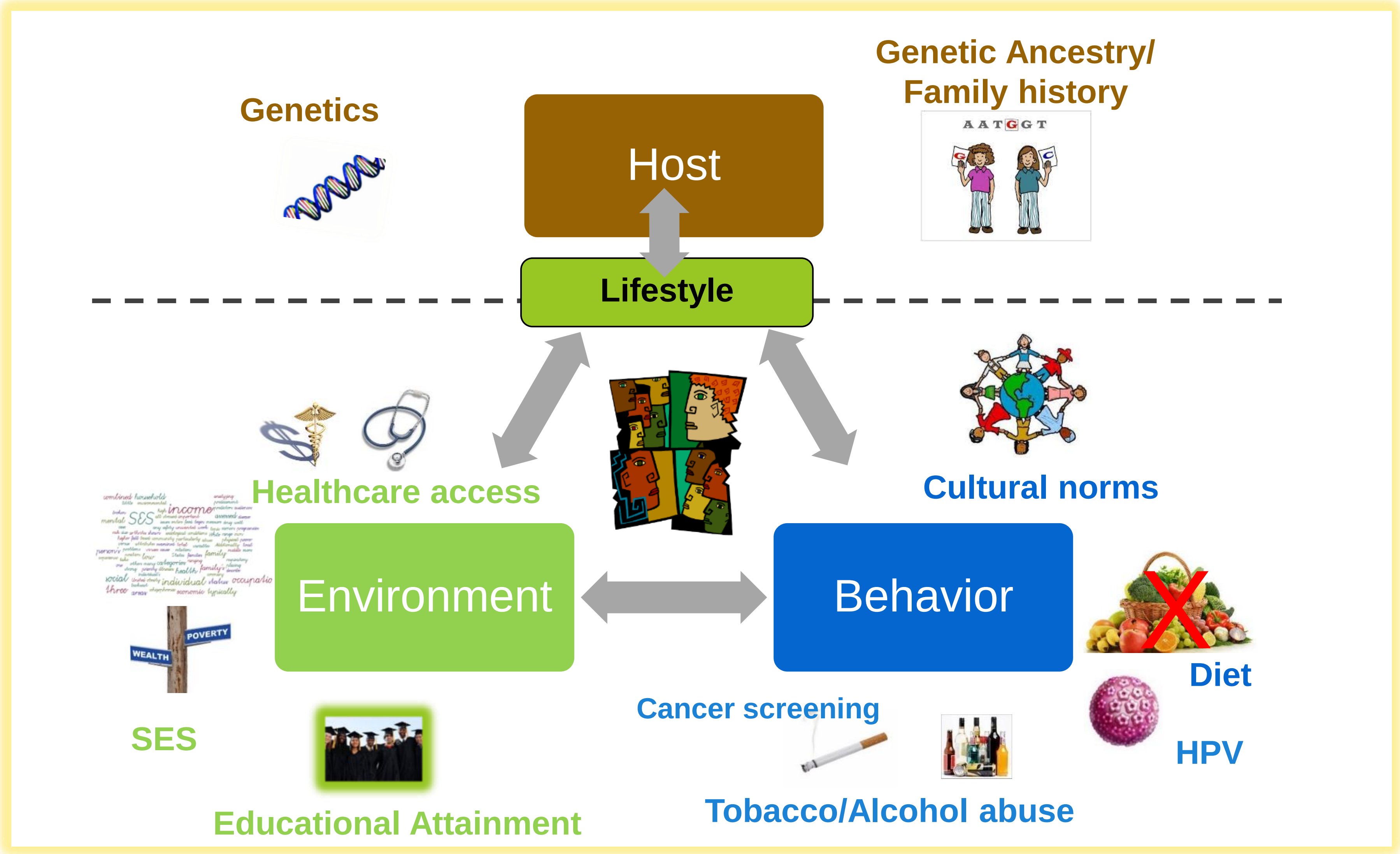
2020

1. Heart disease
2. Cancer
3. Accidents (unintentional injuries)
4. Chronic lower respiratory diseases
5. Stroke (cerebrovascular diseases)
6. Alzheimer's disease
7. Diabetes
8. Influenza and pneumonia
9. Nephritis
10. Intentional self-harm (suicide)



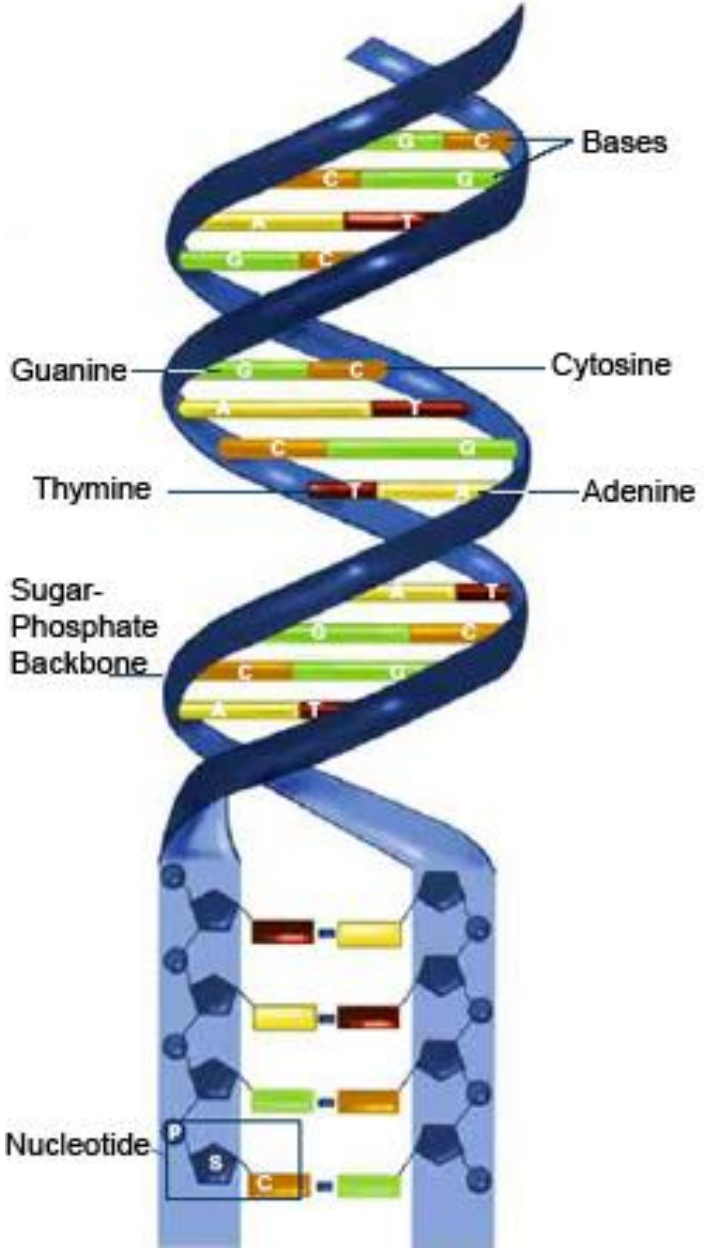
Mathers et al. Global and Regional Causes of Death: Patterns and Trends, 2000–2015

Contributing Factors for Disparities in Cancer



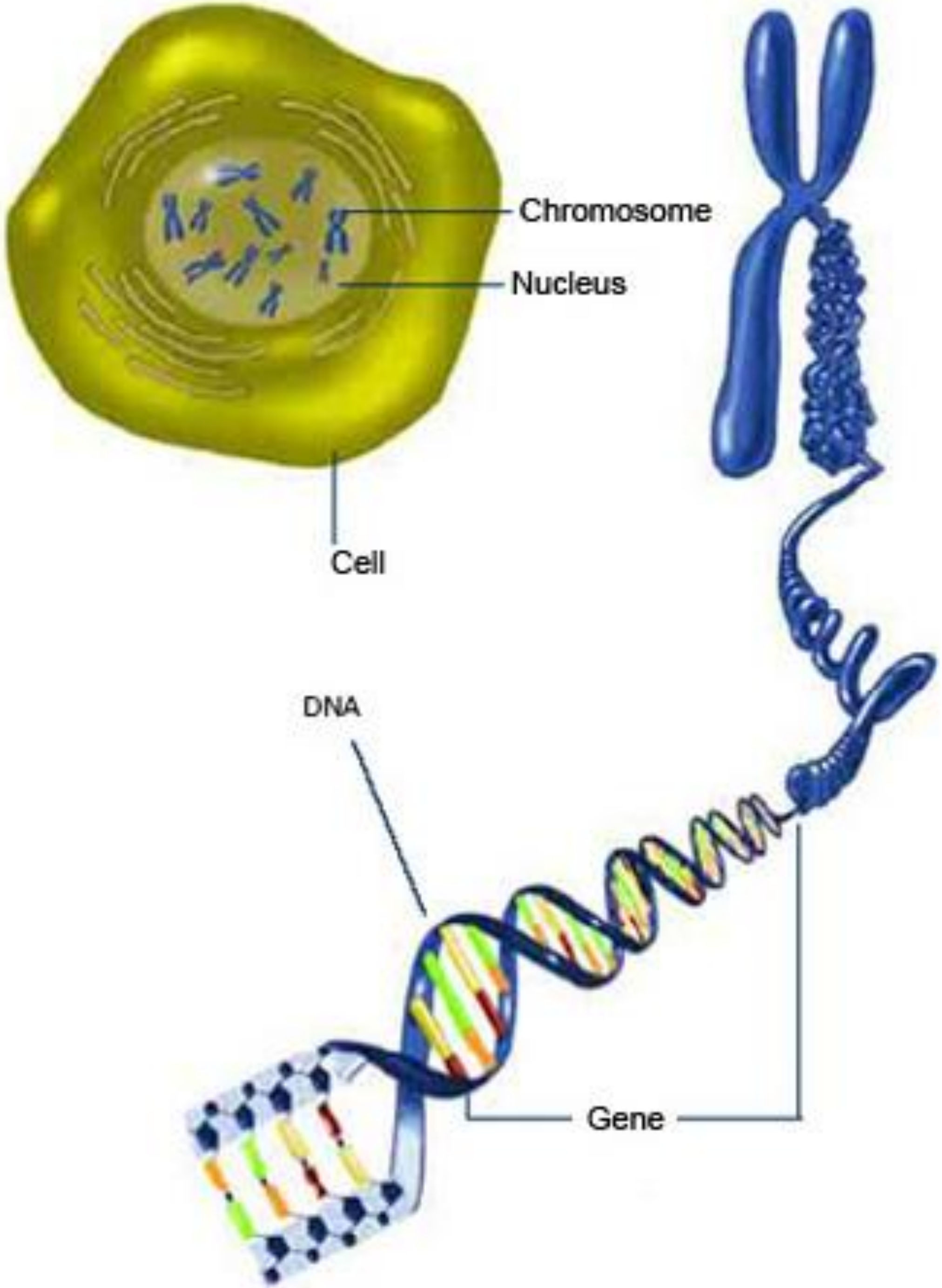
Genetics 101

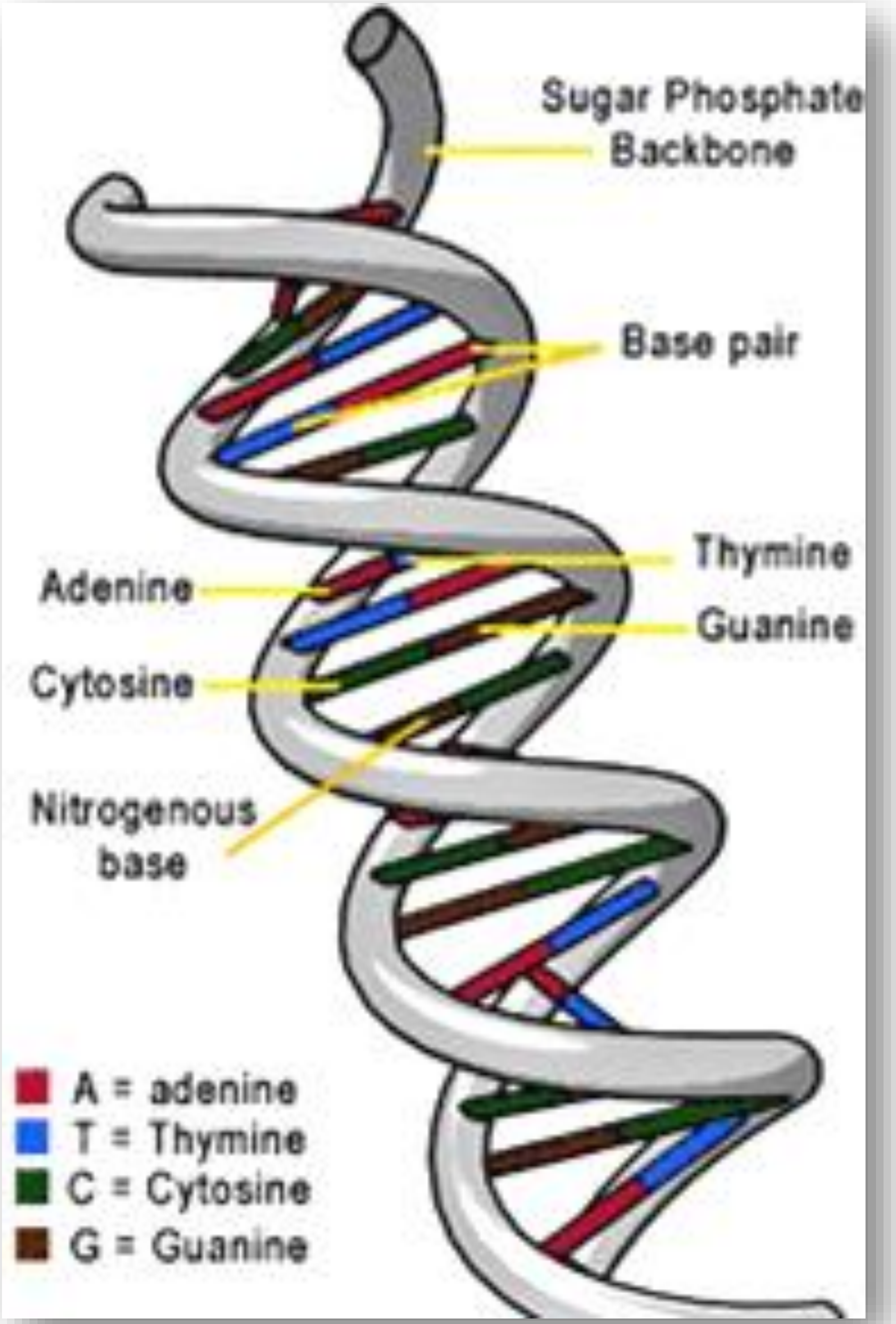
- DNA (deoxyribonucleic acid) is the molecular basis of genetics
- Composed of individual bases, that form base pairs



DNA

- Contained in the nucleus
- Arranged in 22 chromosomes,
  - plus sex chromosomes (X and/or Y)
- Two copies of each
- DNA strand in a single cell
  - Stretched out 6 ft long
- Therefore, very tightly packed





Genetics 101

5' C-G-A-T-T-G-C-A-A-C-G-A-T-G-C 3'
| | | | | | | | | | | | | | |
3' G-C-T-A-A-C-G-T-T-G-C-T-A-C-G 5'

↓

Gene

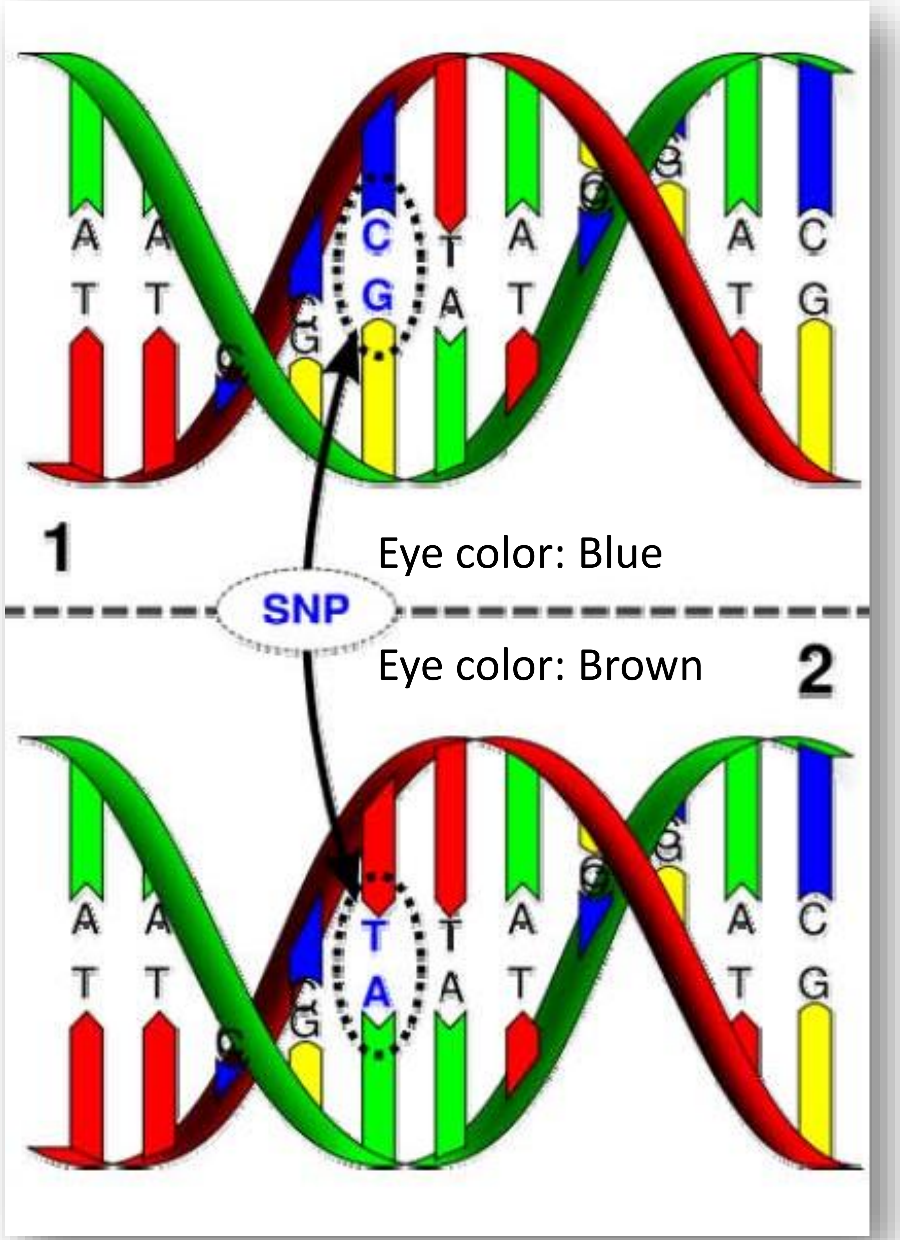
↓

Trait (eye color)

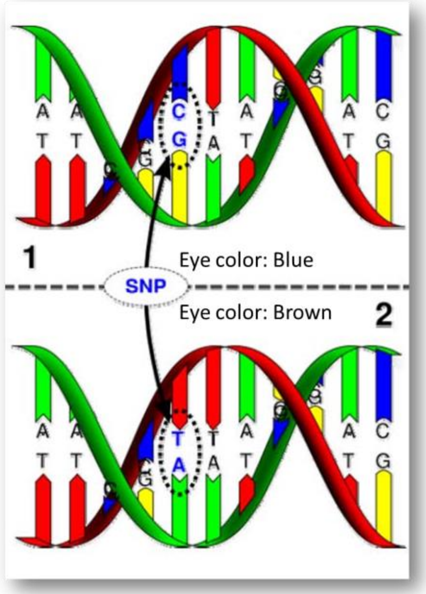
Genetics 101

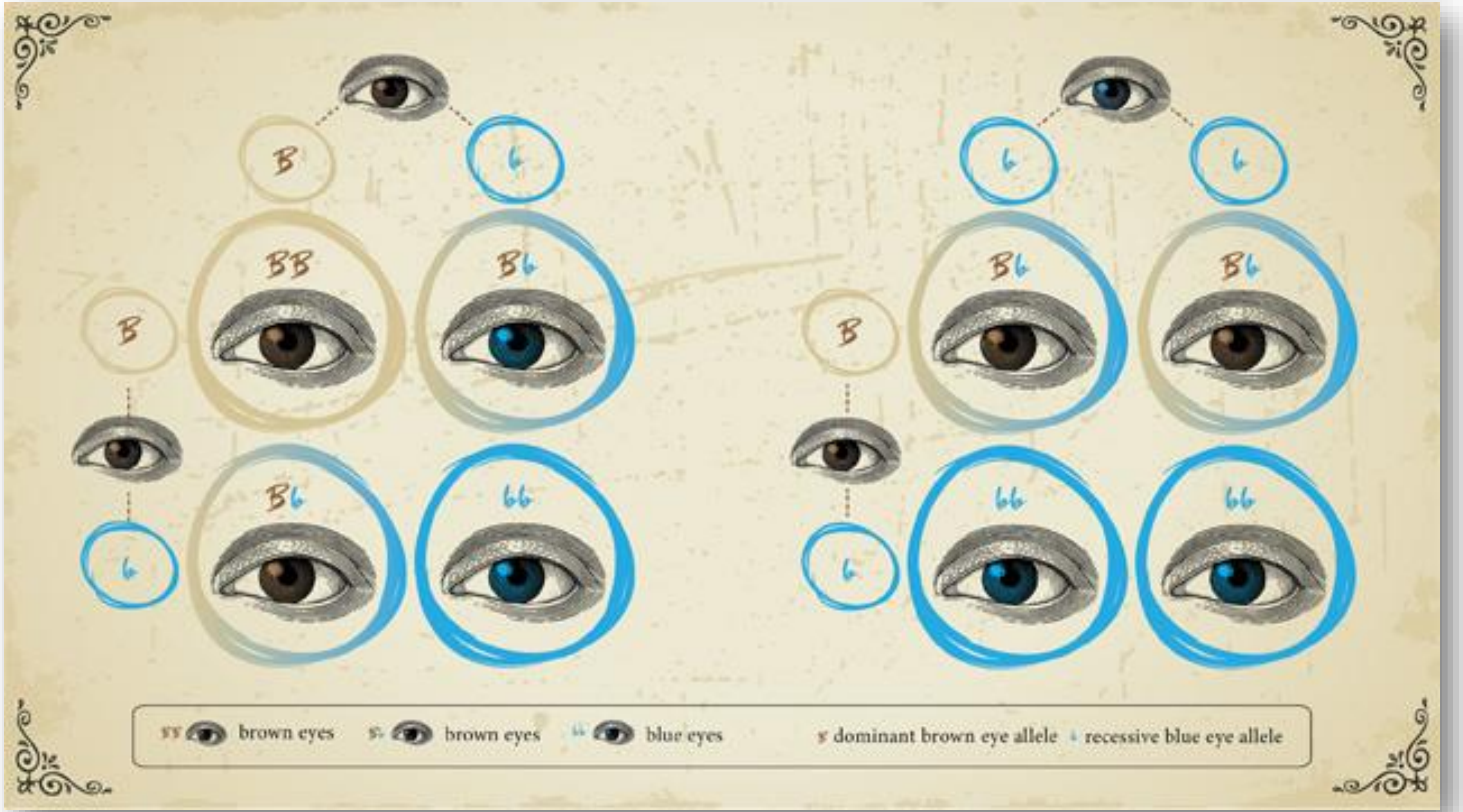
- **Variation** - Single Nucleotide Polymorphisms (SNP) , single nucleotide change within a person's DNA sequence

- Common base changes expressed in the population



Genetic Diversity

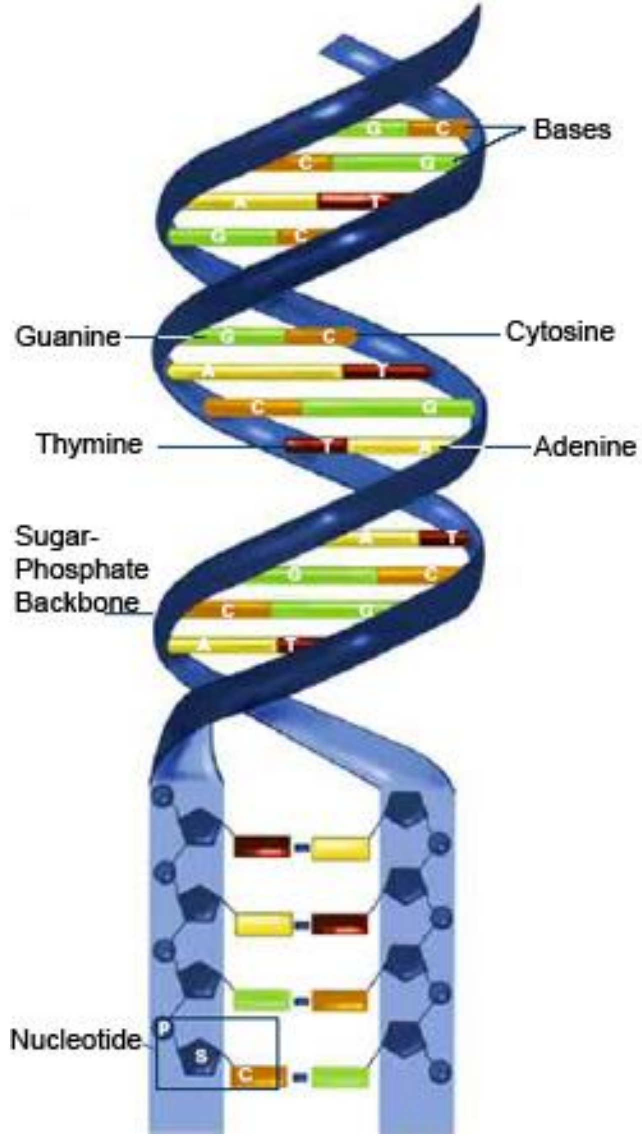




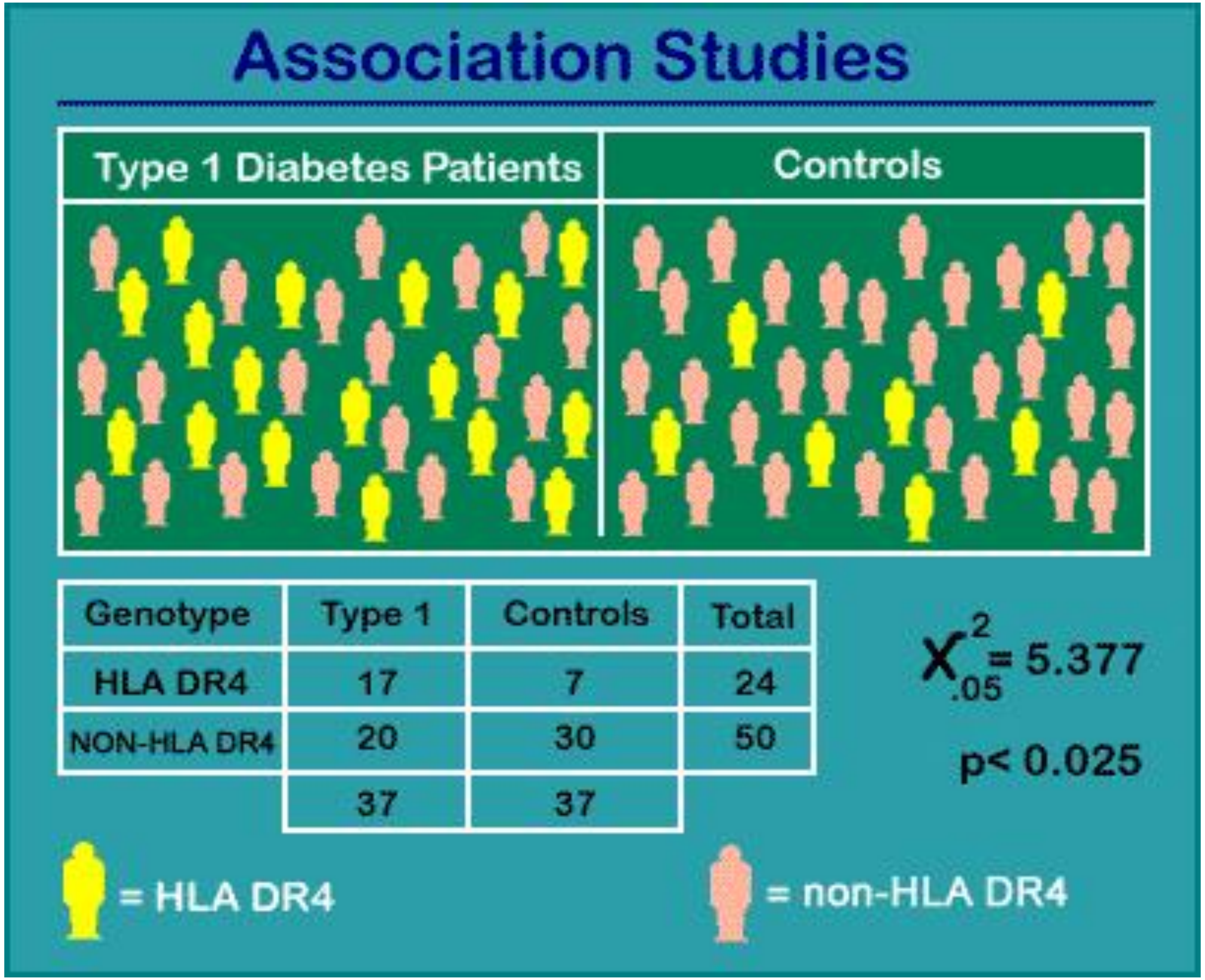
Molly Campbell. Genomics Research from Technology Networks

Genetic Diversity - Biological Differences

- Inherit differences
- An individuals genetic composition
  - insight to the etiology of disease and other preventative or intervention methods



Cases and unrelated population controls from the same study base



Odds Ratio: 3.6
95% CI = 1.3 to 10.4

Genetic variations can impact disease association

Carcinogenesis vol.32 no.9 pp.1361 1365, 2011
doi:10.1093/carcin/bgr119
Advance Access publication June 24, 2011

Multi-institutional prostate cancer study of genetic susceptibility in populations of African descent

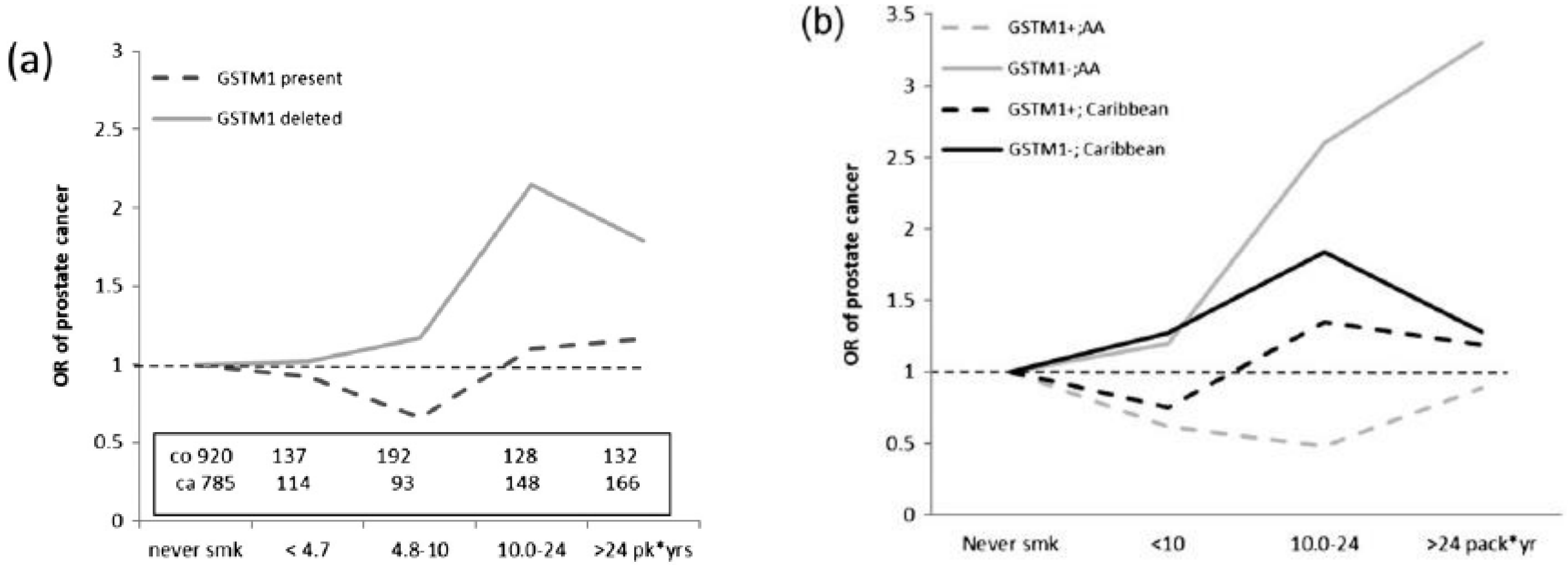


Fig. 1. Association prostate cancer and smoking dose according to GSTM1 status, overall (a) and according to place of origin (b).

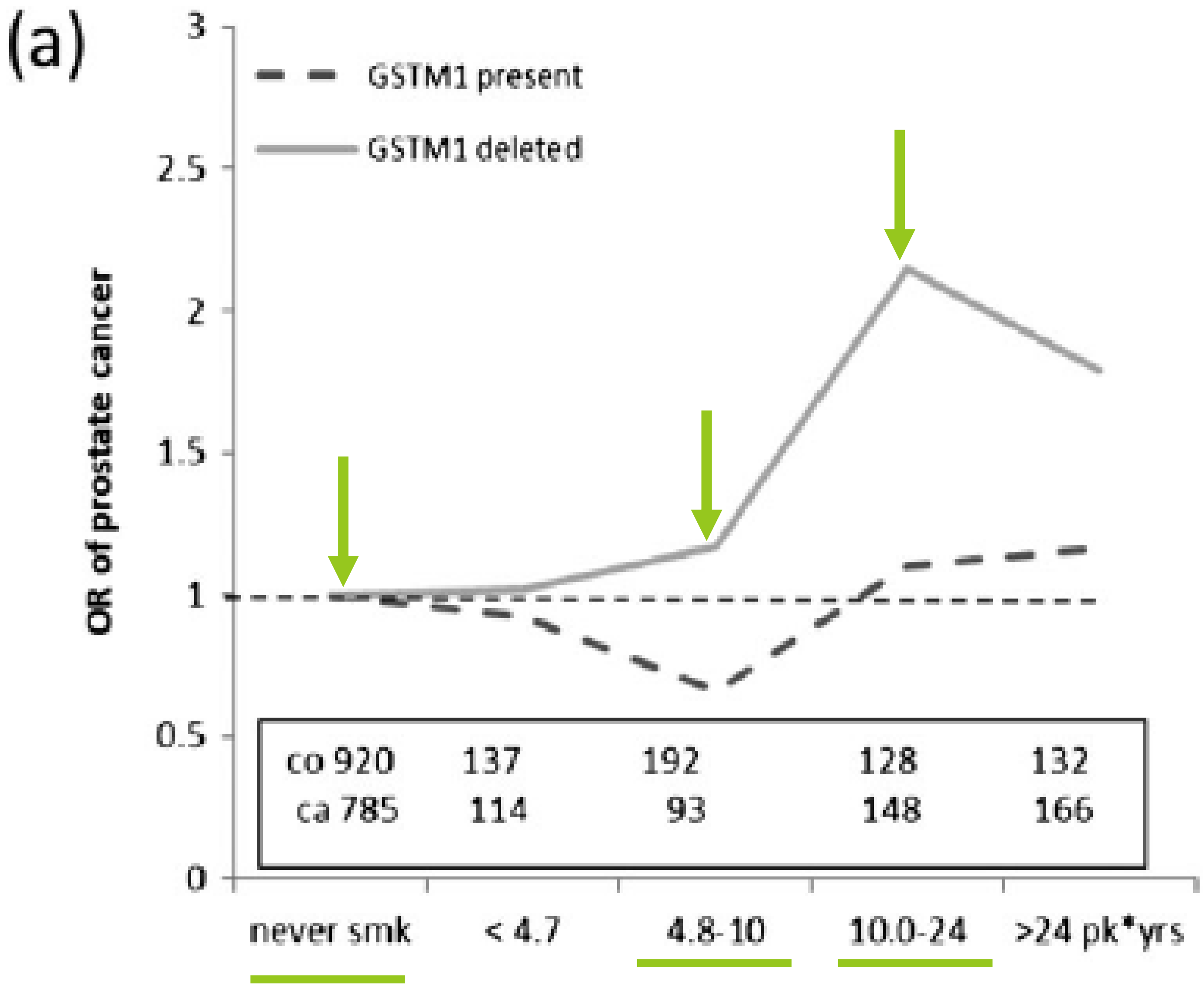
1,715 cases and 2,363 controls: 467 USA; 1,168 Caribbean; 80 Africa

Other factors unique to Caribbean men may be modulating risk

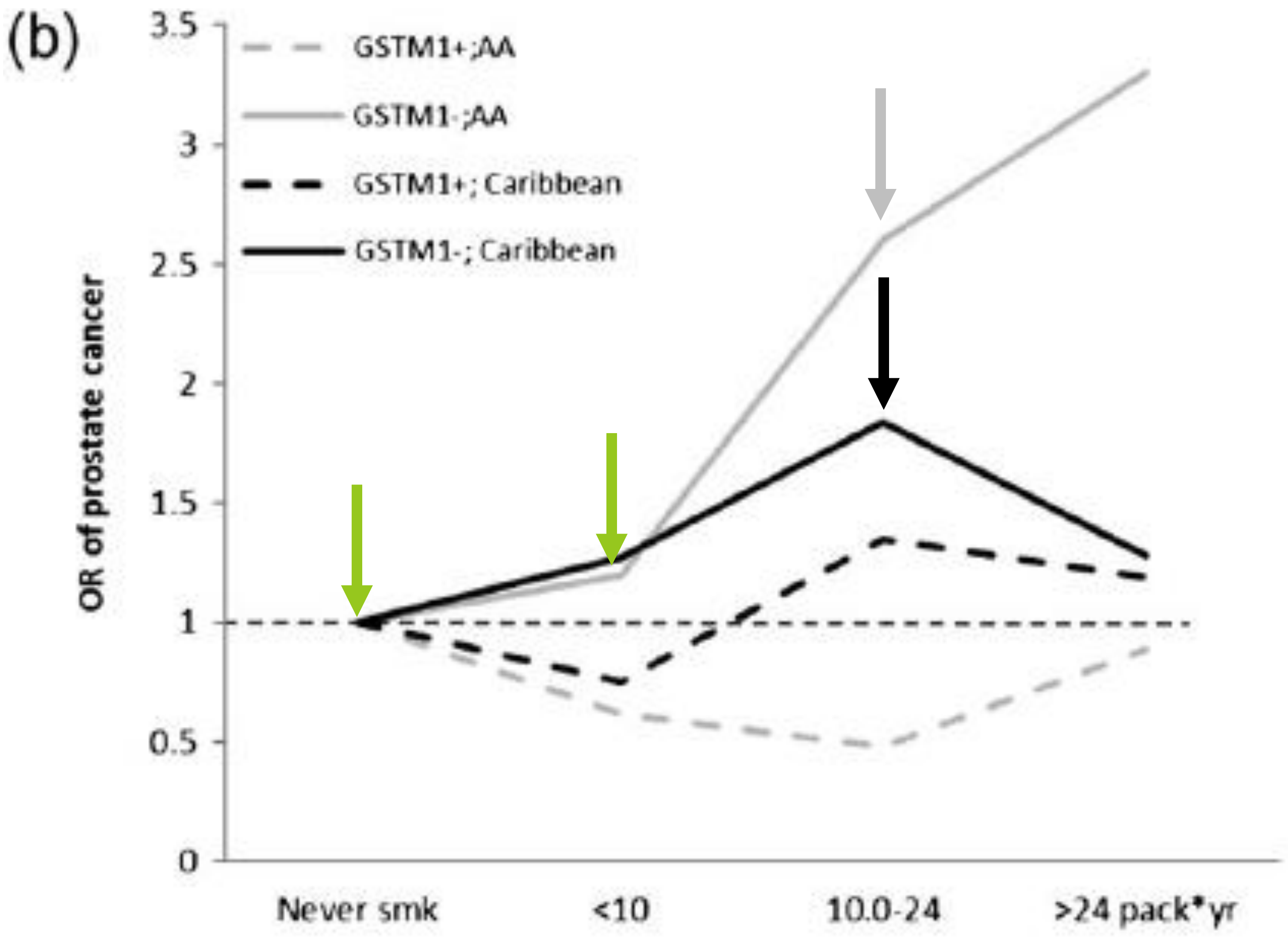
-Smoking prevalence in Caribbean men is similar to AA

-Exposure to other carcinogens that may saturate the GST system, therefore becoming less available for tobacco metabolism.

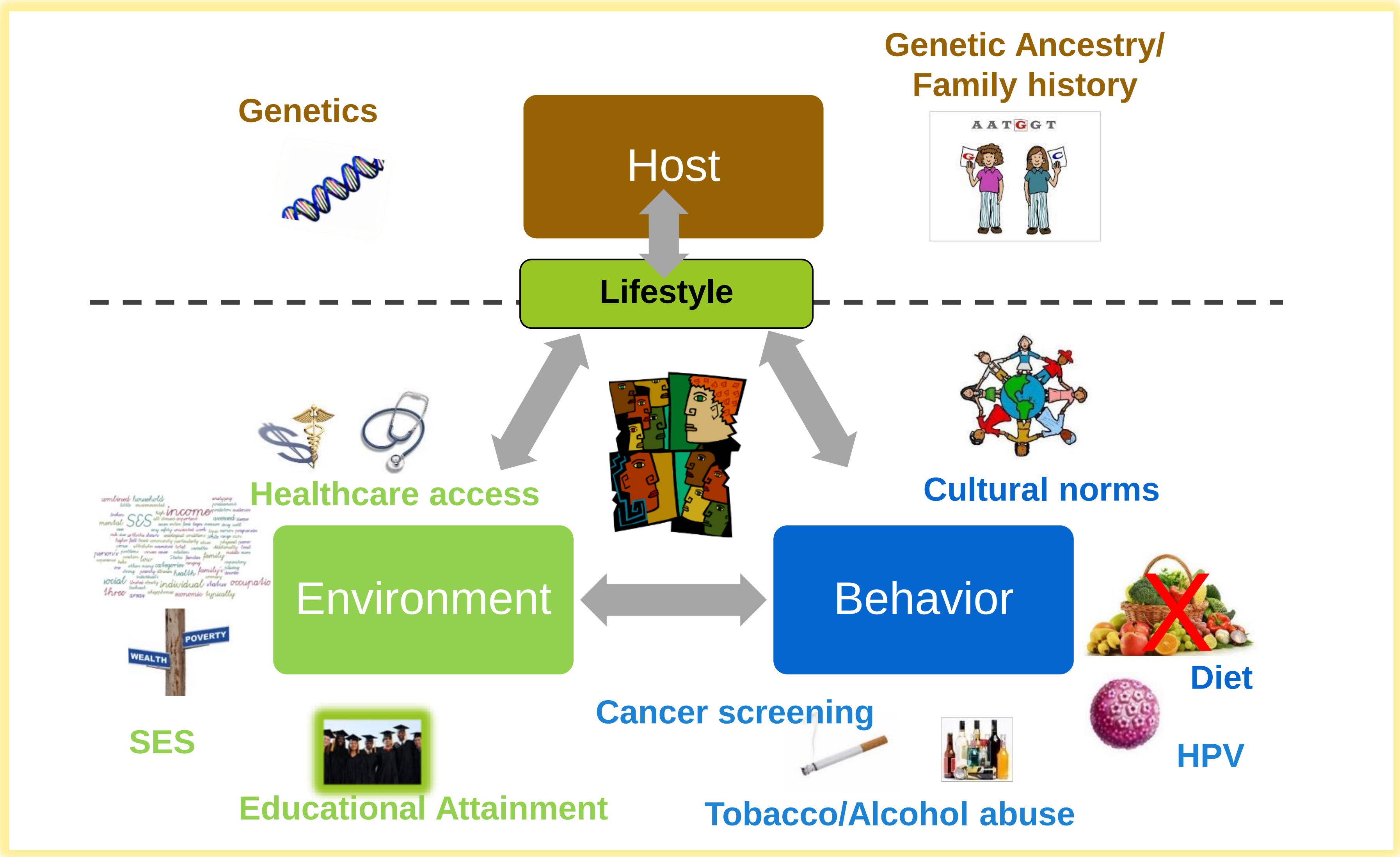
- Same genetic polymorphism but different risk based on behavior
  - never smoker,
  - 4.8-10 pack-years,
  - 10-24 pack-years



- Same genetic polymorphism but different risk based on environment
- USA
- Caribbean

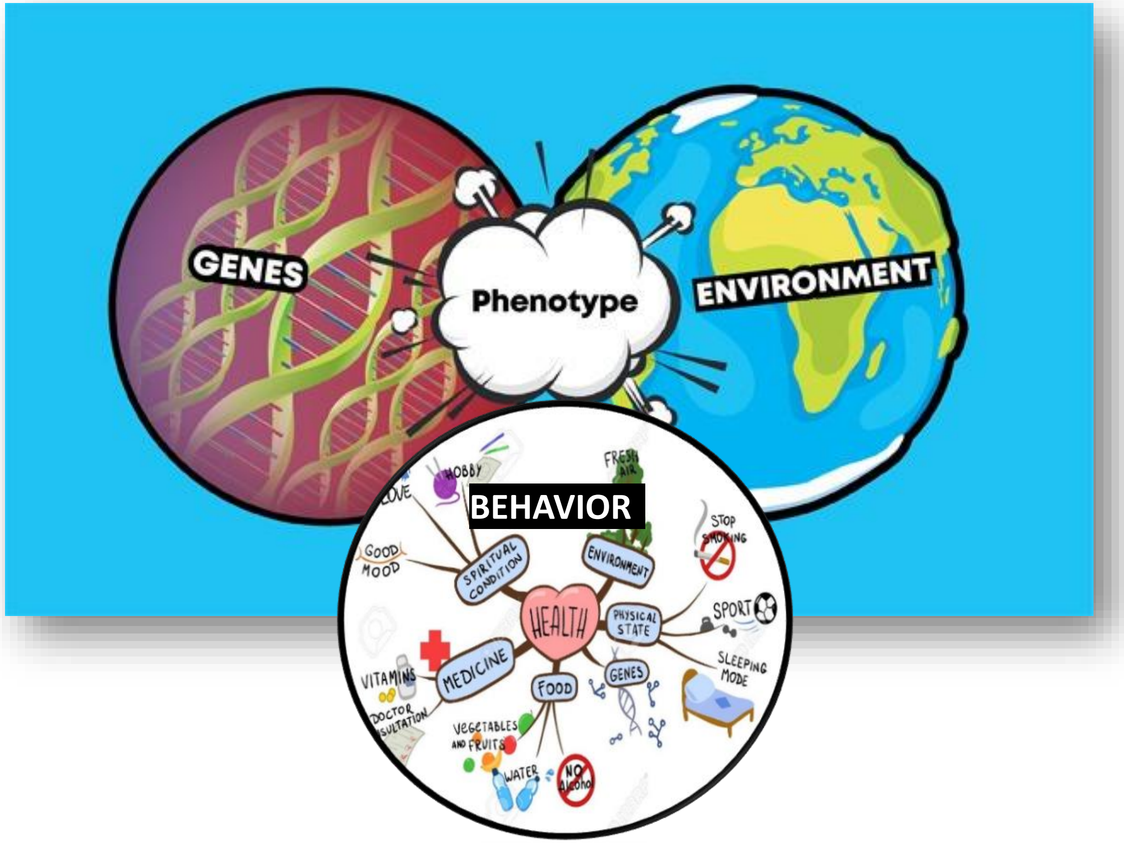


Contributing Factors for Cancer Disparities is Complex



Comparative studies in diverse communities can help to disentangle influences of genetics, behavior and environment !!

Genetic Diversity - Biological Differences



Adapted from : Molly Campbell. Genomics Research from Technology Networks

- An individual's genetic composition <u>alone</u> does not provide full insight to the etiology of disease and other preventative or intervention methods
- Studying diverse community samples does!!
  - Helps to understand modulating effects of behavior and environment on disease

Lecture #2
Genetic Diversity Effects on Disease

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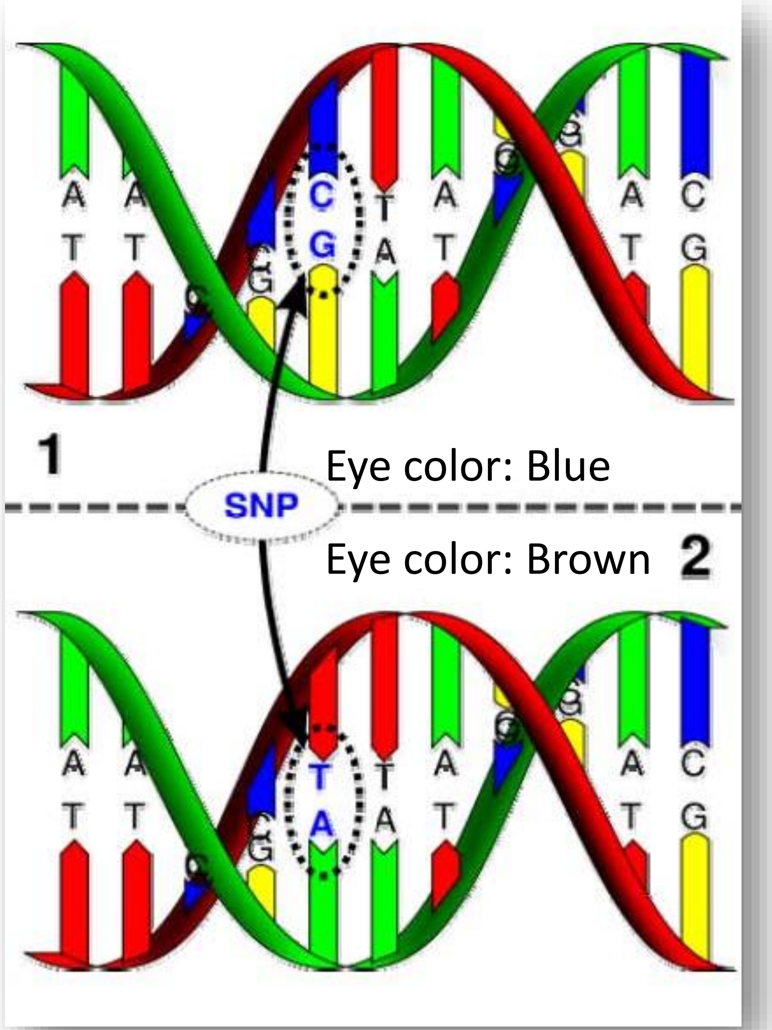
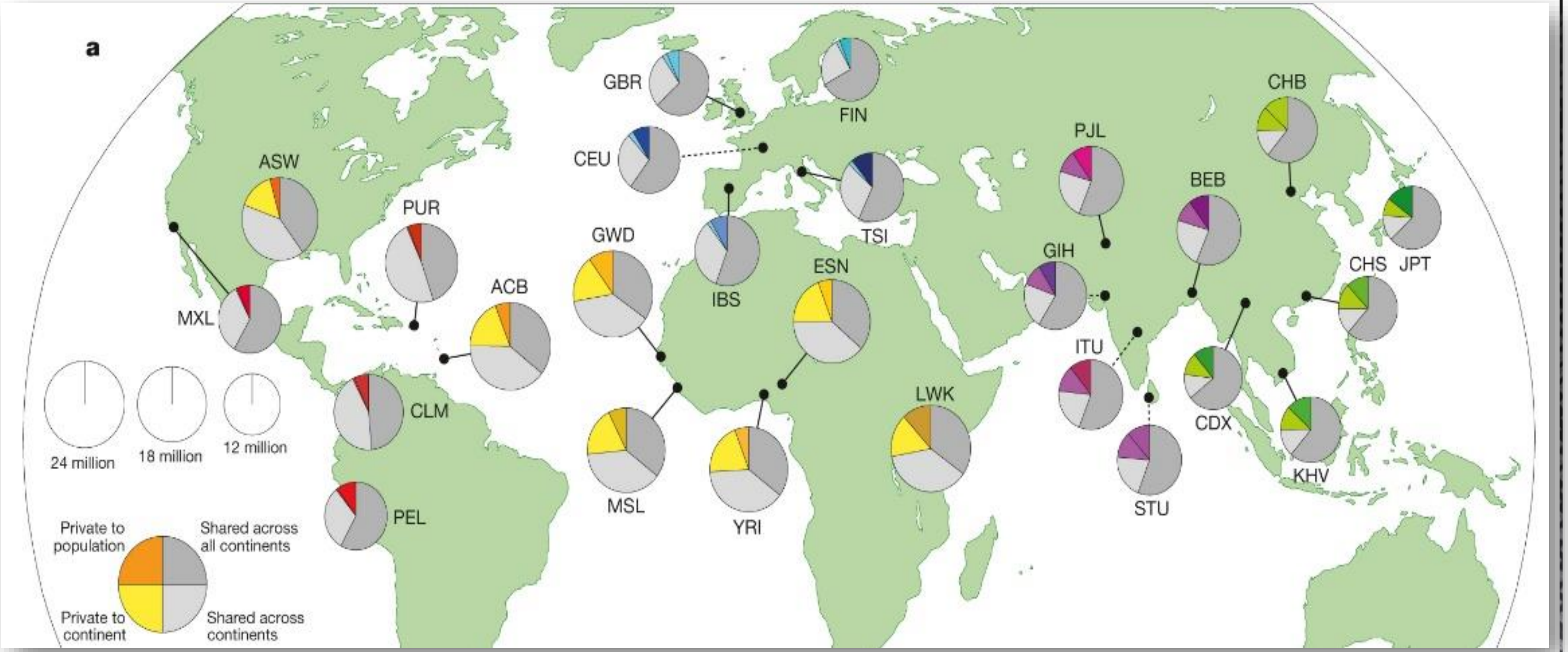
Genetic Variation Contributes to Diversity

- **Variation** - Single Nucleotide Polymorphisms (SNP) , single nucleotide change within a person's DNA sequence

- Common base changes expressed in the population



Genetic Diversity Around the World



nature

A Auton *et al*. *Nature* **526**, 68-74 (2015) doi:10.1038/nature15393

Genetic Diversity Around the World

Population		Code	Population Color	Continental Group Color	Analysis Panel	Phase 1	Phase 3
African ancestry							
Esan in Nigeria	Esan	ESN			AFR		99
Gambian in Western Division, Mandinka	Gambian	GWD			AFR		113
Luhya in Webuye, Kenya	Luhya	LWK			AFR	97	99
Mende in Sierra Leone	Mende	MSL			AFR		85
Yoruba in Ibadan, Nigeria	Yoruba	YRI			AFR	88	108
African Caribbean in Barbados	Barbadian	ACB			AFR/AMR		96
People with African Ancestry in Southwest USA	African-American SW	ASW			AFR/AMR	61	61
Americas							
Colombians in Medellin, Colombia	Colombian	CLM			AMR	60	94
People with Mexican Ancestry in Los Angeles, CA, USA	Mexican-American	MXL			AMR	66	64
Peruvians in Lima, Peru	Peruvian	PEL			AMR		85
Puerto Ricans in Puerto Rico	Puerto Rican	PUR			AMR	55	104
East Asian ancestry							
Chinese Dai in Xishuangbanna, China	Dai Chinese	CDX			EAS		93
Han Chinese in Beijing, China	Han Chinese	CHB			EAS	97	103
Southern Han Chinese	Southern Han Chinese	CHS			EAS	100	105
Japanese in Tokyo, Japan	Japanese	JPT			EAS	89	104
Kinh in Ho Chi Minh City, Vietnam	Kinh Vietnamese	KHV			EAS		99
European ancestry							
Utah residents (CEPH) with Northern and Western European ancestry	CEPH	CEU			EUR	85	99
British in England and Scotland	British	GBR			EUR	89	91
Finnish in Finland	Finnish	FIN			EUR	93	99
Iberian Populations in Spain	Spanish	IBS			EUR	14	107
Toscani in Italia	Tuscan	TSI			EUR	98	107
South Asian ancestry							
Bengali in Bangladesh	Bengali	BEB			SAS		86
Gujarati Indians in Houston, TX, USA	Gujarati	GIH			SAS		103
Indian Telugu in the UK	Telugu	ITU			SAS		102
Punjabi in Lahore, Pakistan	Punjabi	PJL			SAS		96
Sri Lankan Tamil in the UK	Tamil	STU			SAS		102
Total						**1092**	**2504**

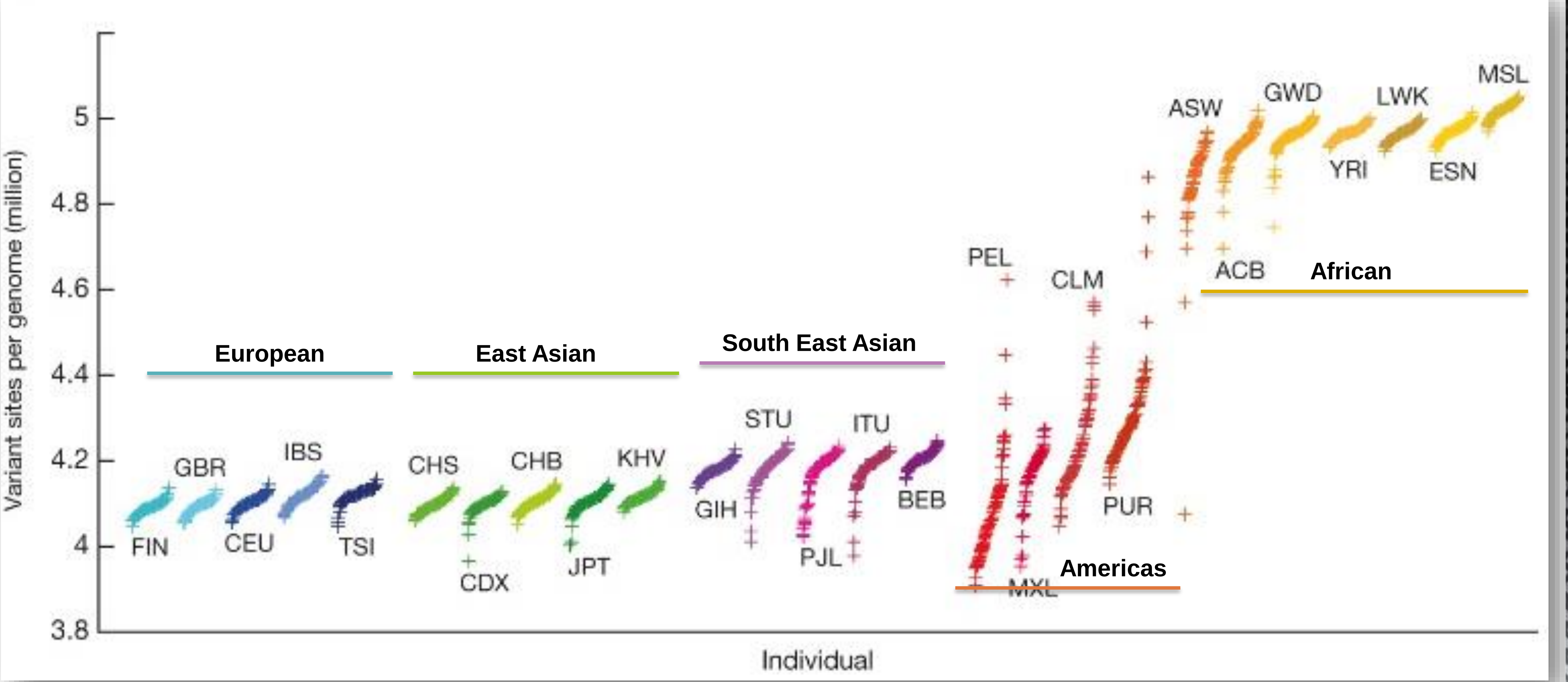
1000 Genomes Project

A Auton *et al*. *Nature* **526**, 68-74 (2015) doi:10.1038/nature15393

nature

Genetic Diversity Around the World

Number of Variant Sites per Genome ranges from 4 million (European) to 5 million (African)



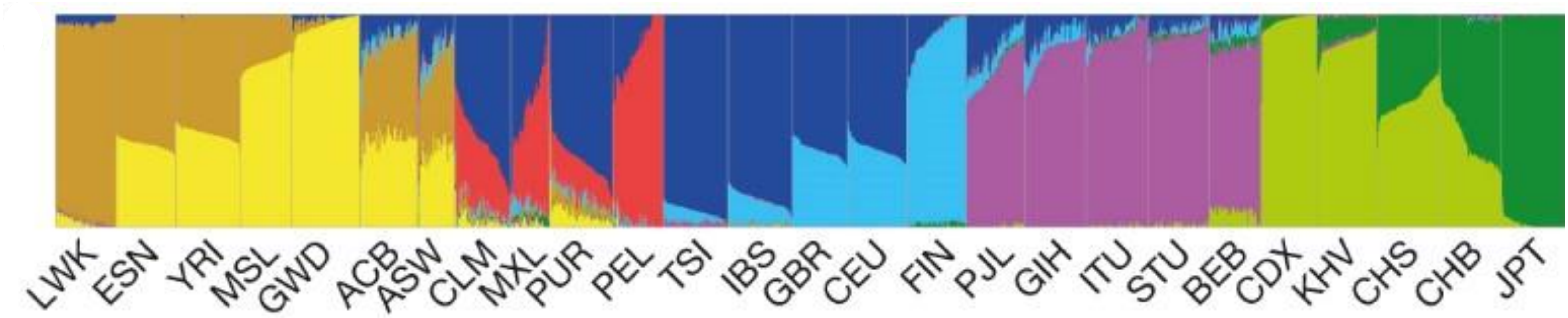
A Auton *et al*. *Nature* **526**, 68-74 (2015) doi:10.1038/nature15393

nature

Markers of Genetic Diversity Around the World

SNPs that can define racial groups

Ancestry Informative Markers (AIMs)



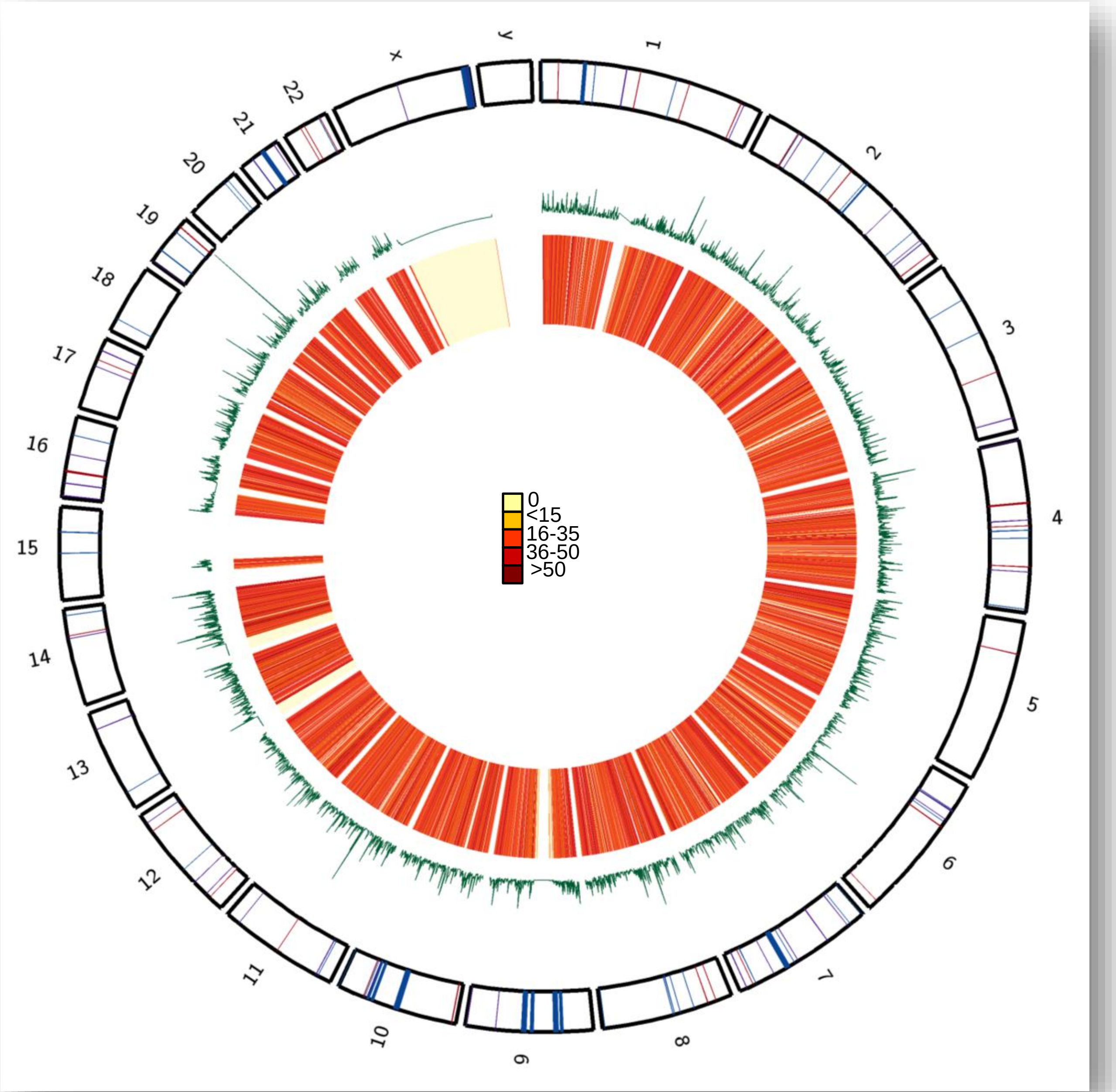
African — Caribbean — African American | Americas | European | South Asian | East Asian

A Auton *et al*. *Nature* **526**, 68-74 (2015) doi:10.1038/nature15393

nature

Genomic Landscape: AIMs that Define African Ancestry

Unique to the African Continent
N = 46,737

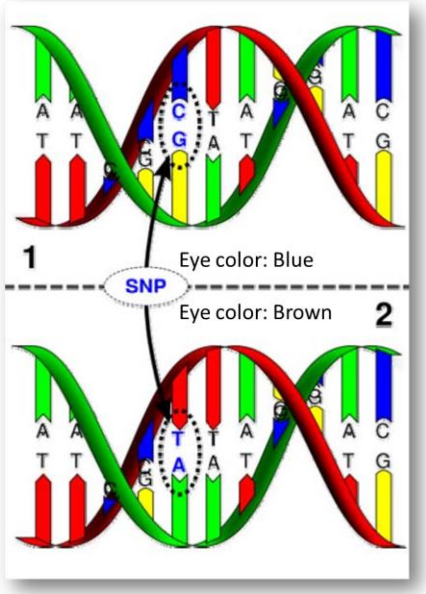


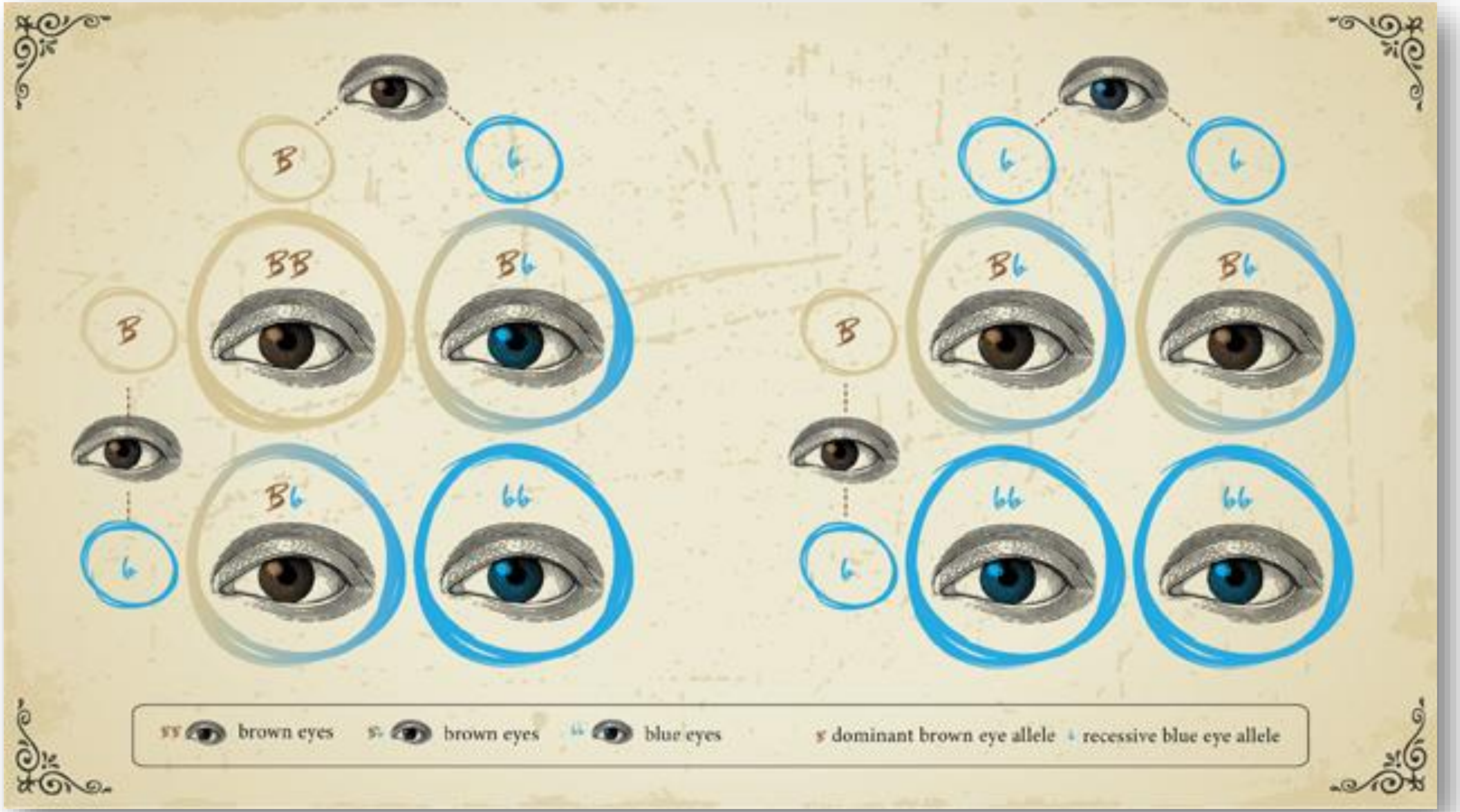
Distribution of AIMs in genes involved in tobacco metabolism. The genes are shown on **chromosome**.

The distribution of AIMs on chromosomes are shown by **line graph** and **heatmap**.

What are some biological effects of genetic variability?

SNPs/AIMs Can Influence Gene Expression





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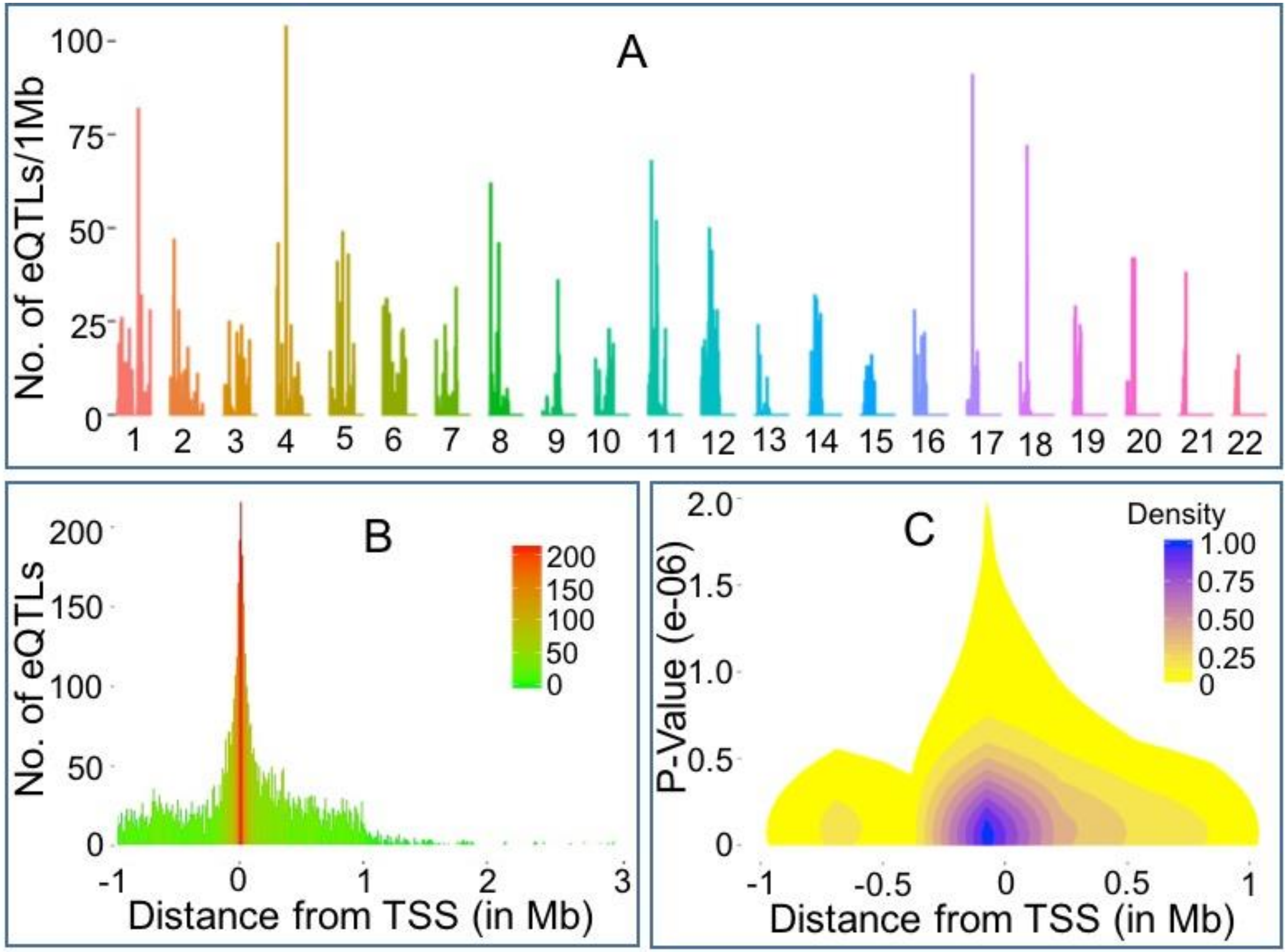
SNPs that Influence Qene Expression (eQTLs)

located in close proximity to transcription start site of genes



cis-eQTLs in oral cavity and laryngeal cancers using TCGA data (N = 268, EA)

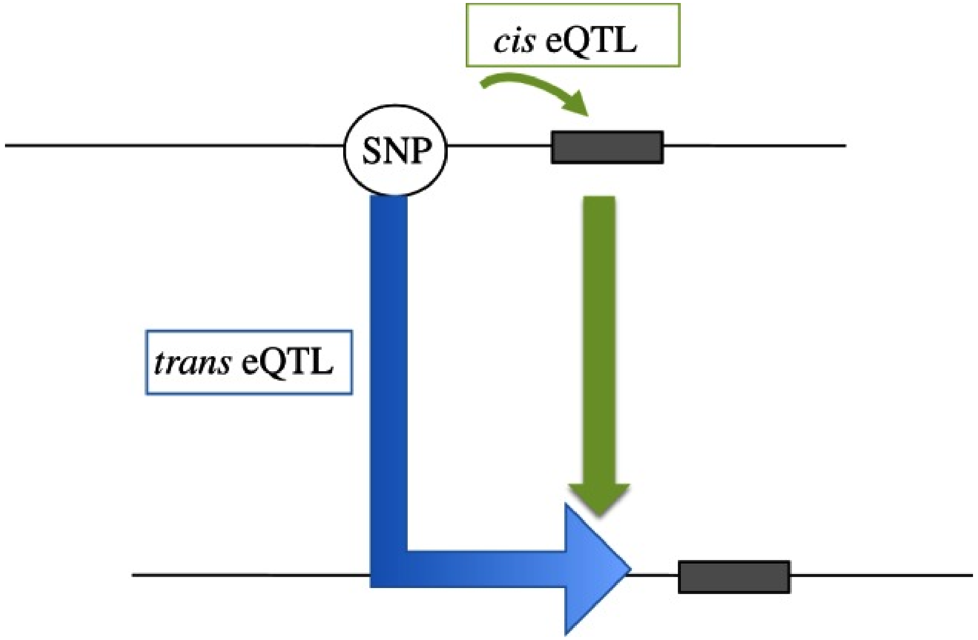
Ramakodi, PhD

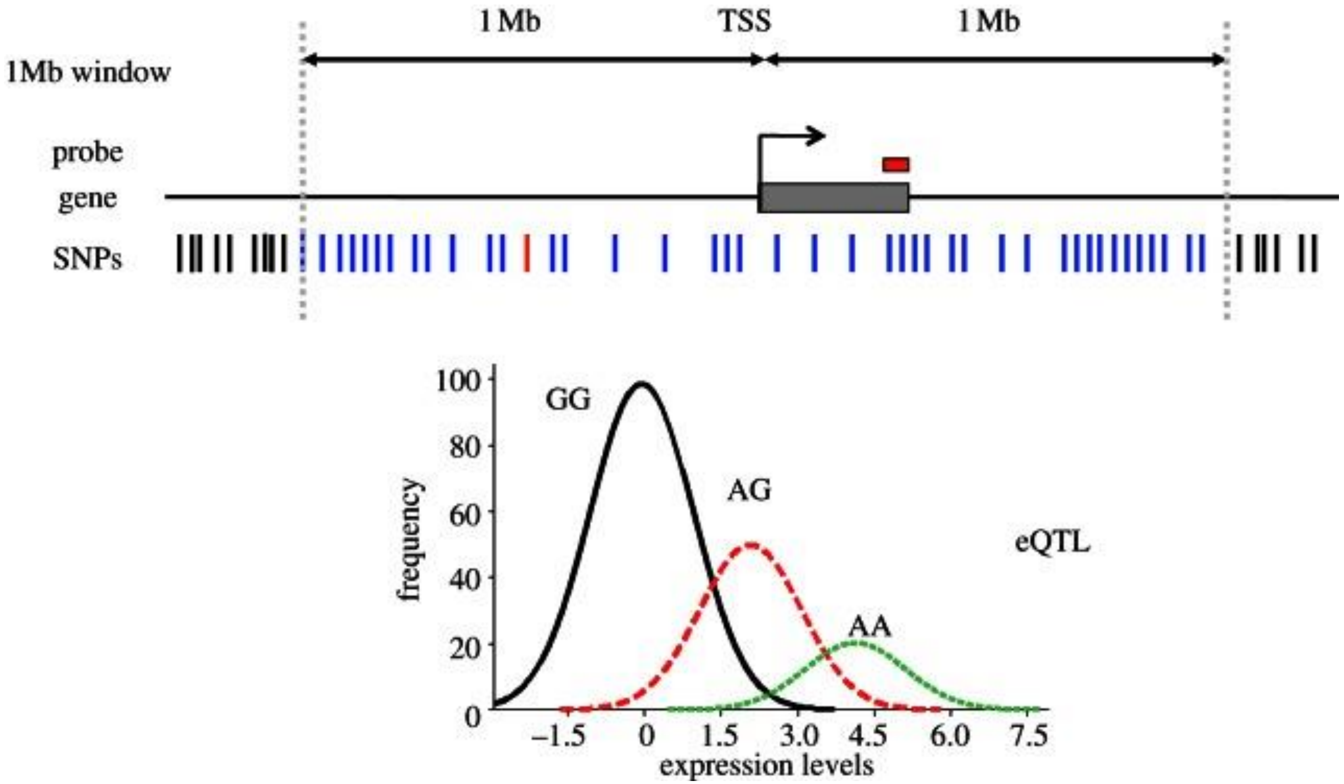
TCGA

NCI | NHGRI

Manuscript in preparation

SNPs/AIMs as Expression Quantitative Trait Loci (eQTLs)





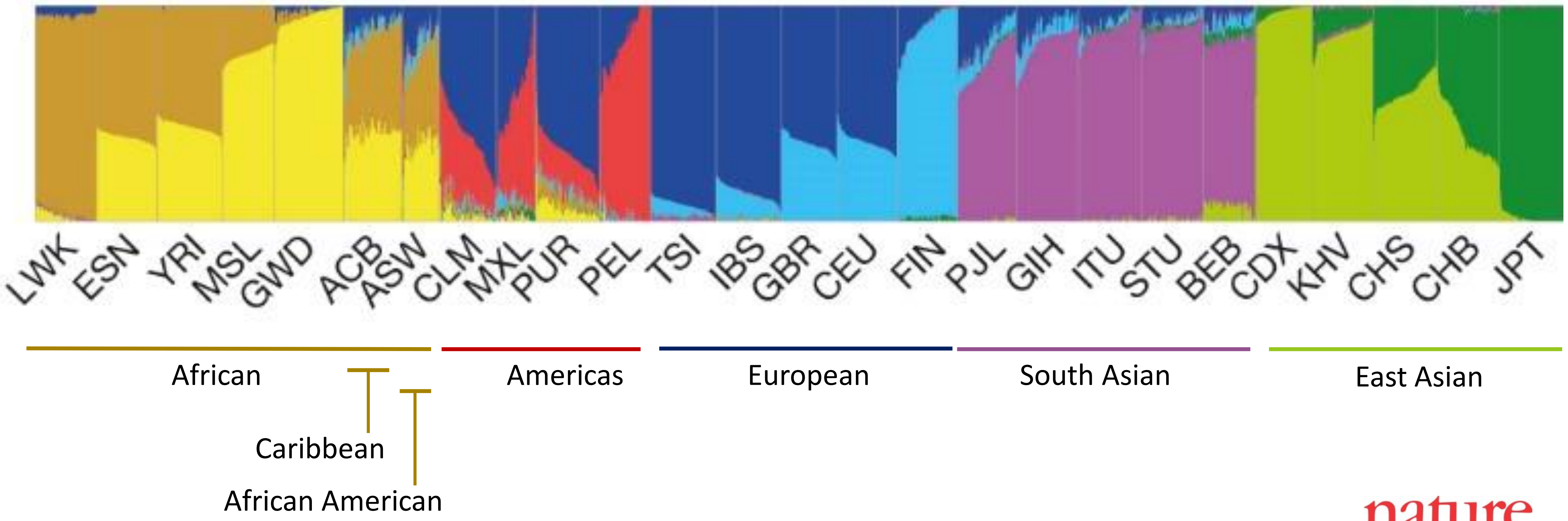
Nica and Dermitzakis, Philos Trans R Soc Lond B Biol Sci. 2013 Jun 19; 368(1620)

Markers of Genetic Diversity Around the World

SNPs that can define racial groups

Ancestry Informative Markers (AIMs)

If some of these AIMs are eQTLs certain genes may express at different levels between populations

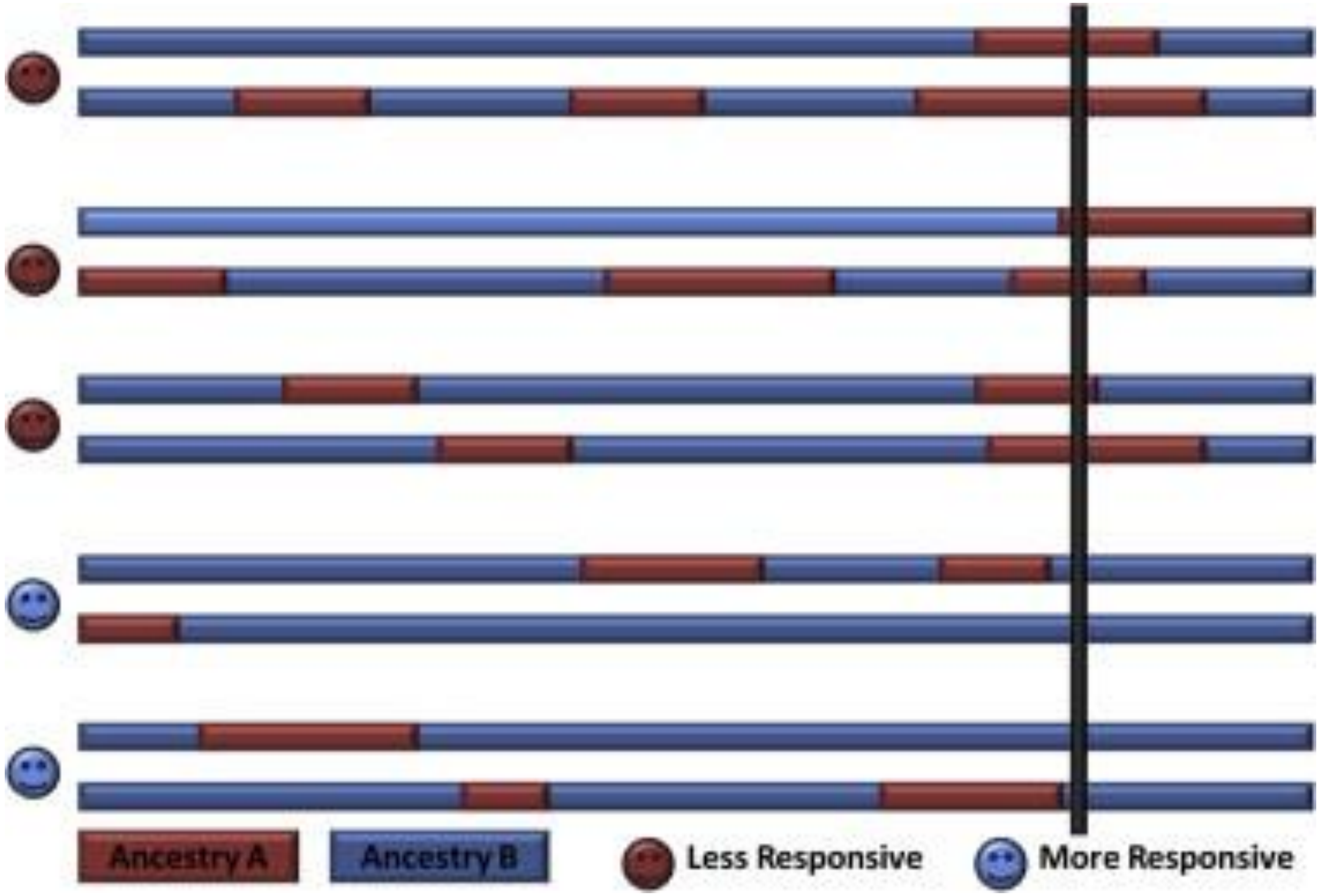


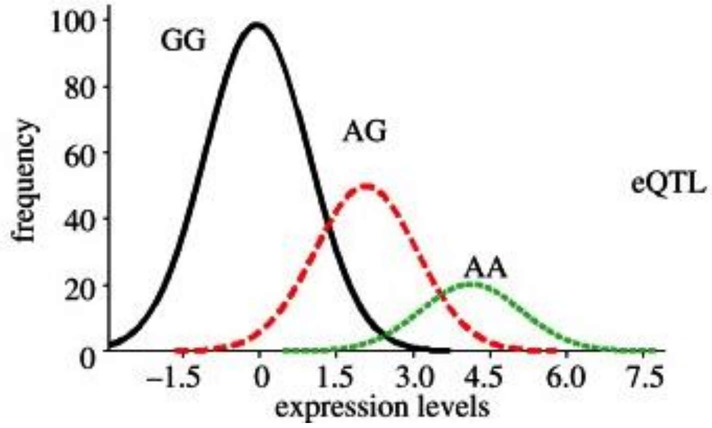
A Auton *et al*. *Nature* **526**, 68-74 (2015) doi:10.1038/nature15393

nature

What if Differentially Expressed Genes are Involved in Metabolizing Medications?

Implications of genetic/genomic variation in communities



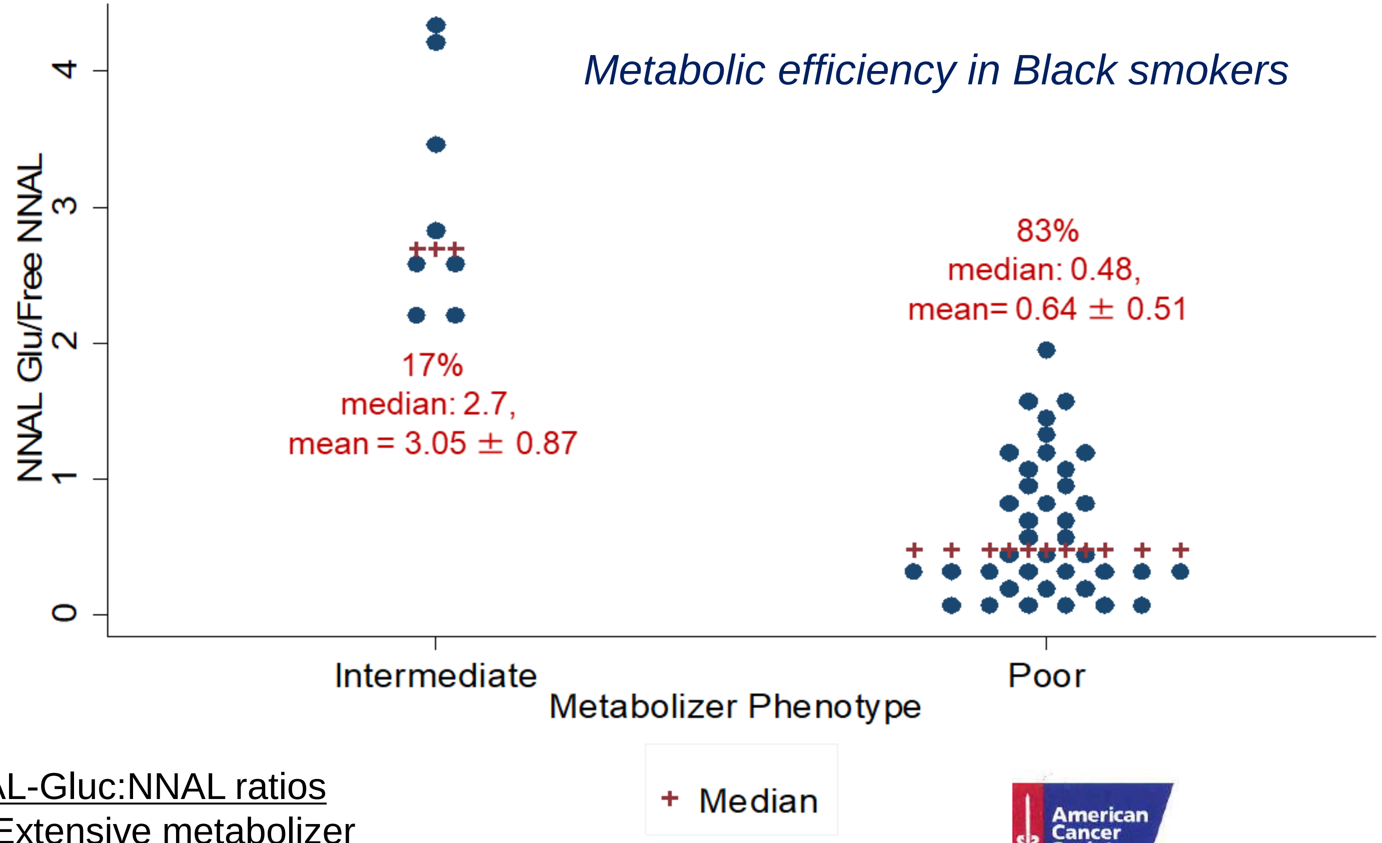


Nica and Dermitzakis, Philos Trans R Soc Lond B Biol Sci. 2013 Jun 19; 368(1620)

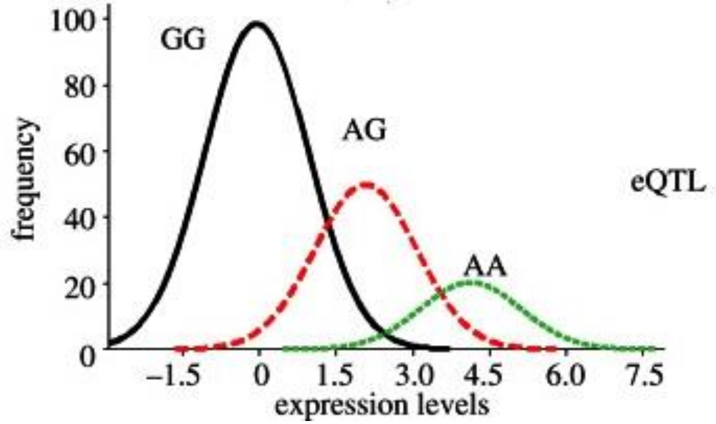
Journal of Allergy and Clinical Immunology, Volume 133, Issue 1, 2014, 16 - 26

What if Differentially Expressed Genes are Involved in Metabolizing Environmental Exposures?

Implications of genetic/genomic variation in communities



e.g. Tobacco metabolism?



Nica and Dermitzakis, Philos Trans R Soc Lond B Biol Sci. 2013 Jun 19; 368(1620)

<u>NNAL-Gluc:NNAL ratios</u>
>5: Extensive metabolizer
2-5: Intermediate metabolizer
<2 : Poor metabolizer

American Cancer Society®

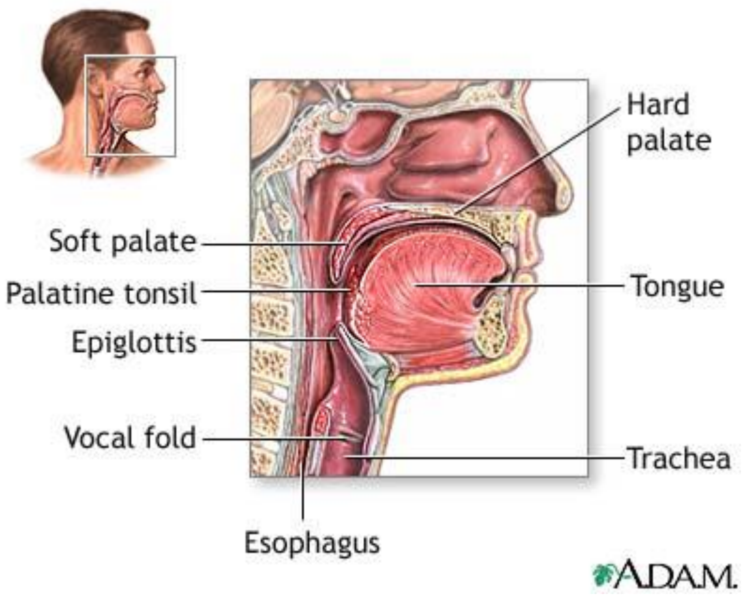
Blackman et al. Ethnicity and Health 2018

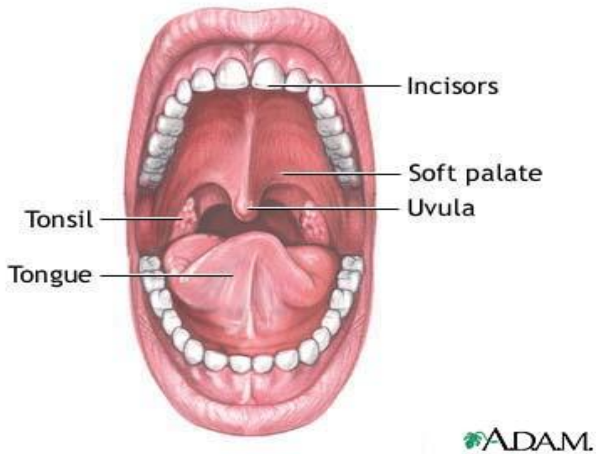
What are some other biological effects of genetic variability?

Lets dig a bit deeper!

Genetic diversity - Biological Differences – Disease

Head and Neck Cancer - Example

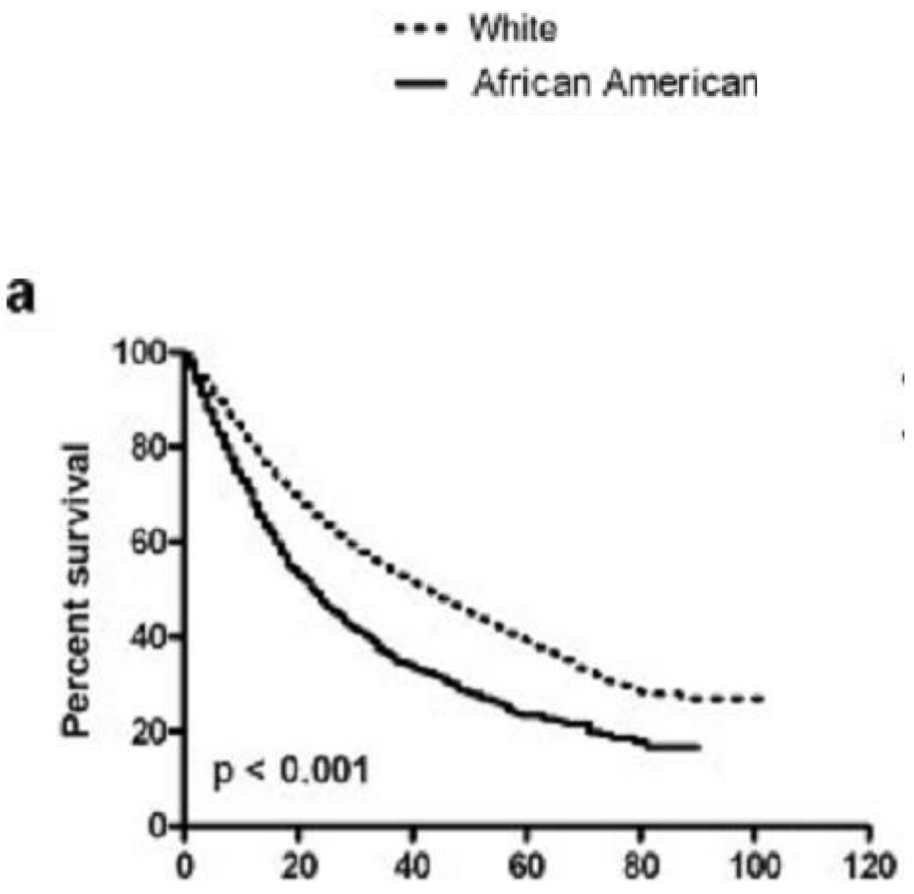




African American and Poor Patients Have a Dramatically Worse Prognosis for Head and Neck Cancer

An Examination of 20,915 Patients

- HNCa patients from 1998-2002 from the Florida Registry
- 21,000 HNCa patients
- Median survival time of 40 months (whites) vs. 21 months (AA)



Multivariate predictors of outcome

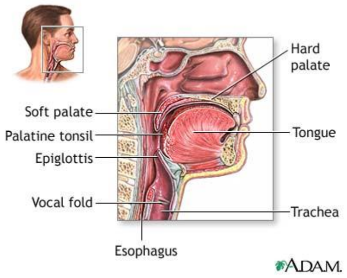
- Race **(OR 1.365 AA)**
- Poverty **(OR 1.313)**
- Age
- Sex **(OR 0.987 Females)**
- Tumor site
- Stage
- Grade
- Treatment
- Smoking/ETOH **(OR 1.336/1.309)**

Molina et al, 2008

Race and SES as driver of survival

Determinants of head and neck cancer survival according to race

Camille C. Ragin, PhD, MPH[1,2,*], Scott M. Langevin, PhD, MHA[2], Mark Marzouk, MD[3], Jennifer R. Grandis, MD[3], and Emanuela Taioli, MD, PhD[1,2]



- Matched single institution retrospective study 1987-2007
  - n=348 3:1 match (AA 87 / EA 261)

- Controlled for age, gender, tobacco use (pack year dose), alcohol use, socioeconomic status, insurance status and subsite site

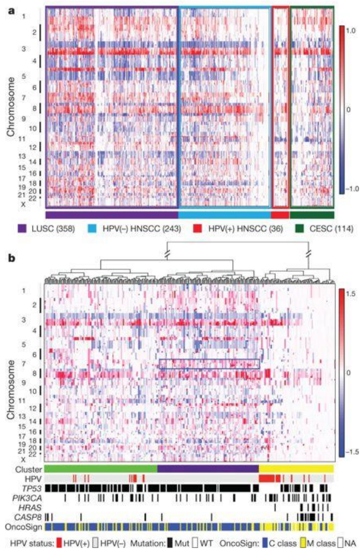
- Relapse-free survival larynx tumors: Black vs. White patients (AdjHR = 3.36, 95% CI: 1.62-7.00)

- **Factors other than socioeconomic status and access to care may contribute to poor relapse-free survival**

Ragin et al, Head and Neck 2011

Implications of Genetic/Genomic Diversity on Biology of a Disease

Mutational landscape of laryngeal cancer



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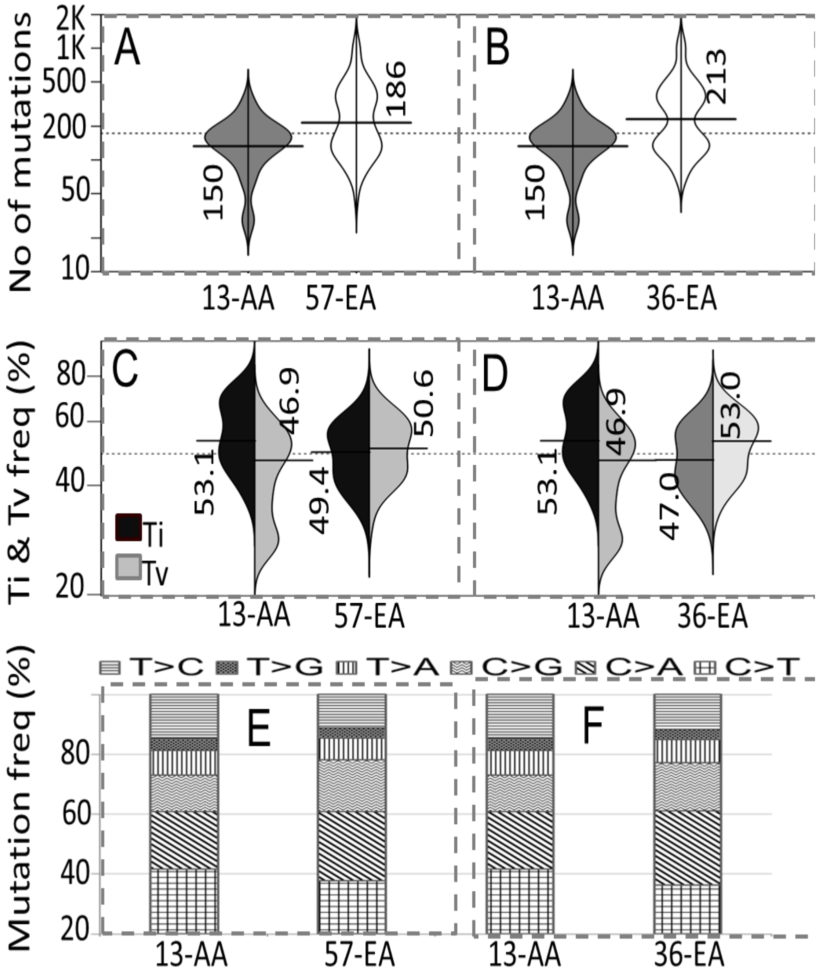
NCI | NHGRI

Diversity of the Normal Genome
Diversity of the Cancer Genome

Somatic Mutation landscape differences by race (Laryngeal cancer)



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Ancestral-derived effects on the mutational landscape of laryngeal cancer

Meganathan P. Ramakodi [a,b,c,d], Rob J. Kulathinal [b,c,d], Yujin Chung [b,d], Ilya Serebriiskii [e,f], Jeffrey C. Liu [a,g], Camille C. Ragin [a,c,g,h,*]

A: All patients

B: Matched –Stage III/IV, median age: 60

cig pack-year: 40(AA), 60(EA)

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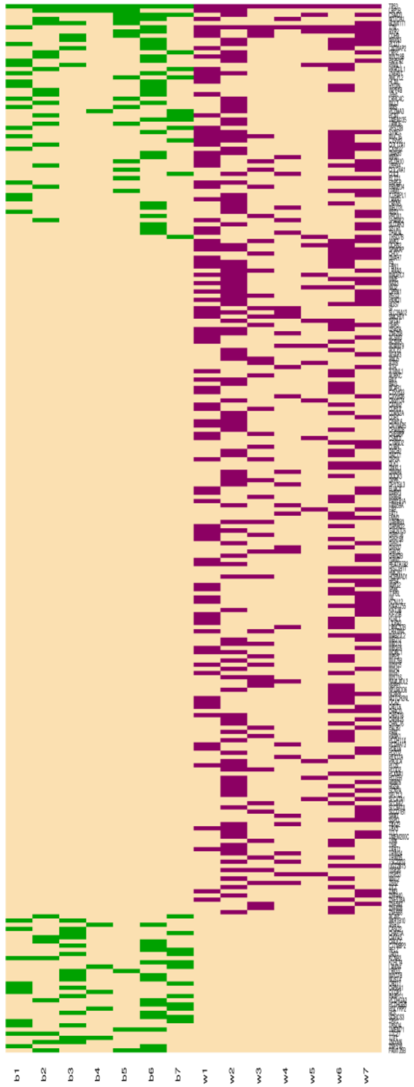
Ramakodi, PhD

Diversity of the Normal Genome
Diversity of the Cancer Genome

Black **White**



Mutation frequencies of genes differed (Black vs. White)

Gene	Afr-Amr (N = 13)	Eur-Amr (N = 36)	P-value
RUNX1T1	5 (38.46%)	3 (8.33%)	0.037
TTN	5 (38.46%)	30 (83.33%)	0.007
NAV3	0 (0%)	13 (36.11%)	0.031
PIK3CA*	0 (0%)	12 (33.33%)	0.043
KIAA1033	3 (23.08%)	0 (0%)	0.021
ZMYM6	3 (23.08%)	0 (0%)	0.021

* Indicates known cancer driver gene from HNSCC.

Ramakodi, PhD

Genomics 2016

- Findings suggest the genomic diversity influences mutational signatures in laryngeal cancer

- The mutational landscape of tumors in Black patients differed than in White patients
  - Somatic mutations occur at different frequencies and is related to significant differences in germline sequence by race
  - Frequency of mutations in cancer driver genes are different by race

- These observations <u>may</u> have strong implications in precision medicine

- Underscores the importance of gentic/genomic research in diverse communities

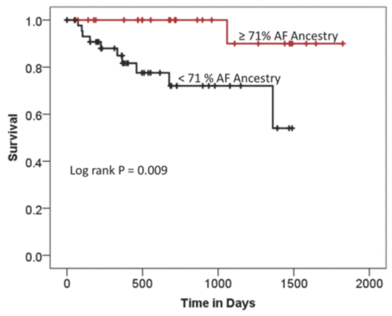
What are some other biological effects of genetic variability?

Another example?

Lets dig a bit deeper!

Implications of Genetic/Genomic Diversity on Disease Outcome

Cis-eQTLs



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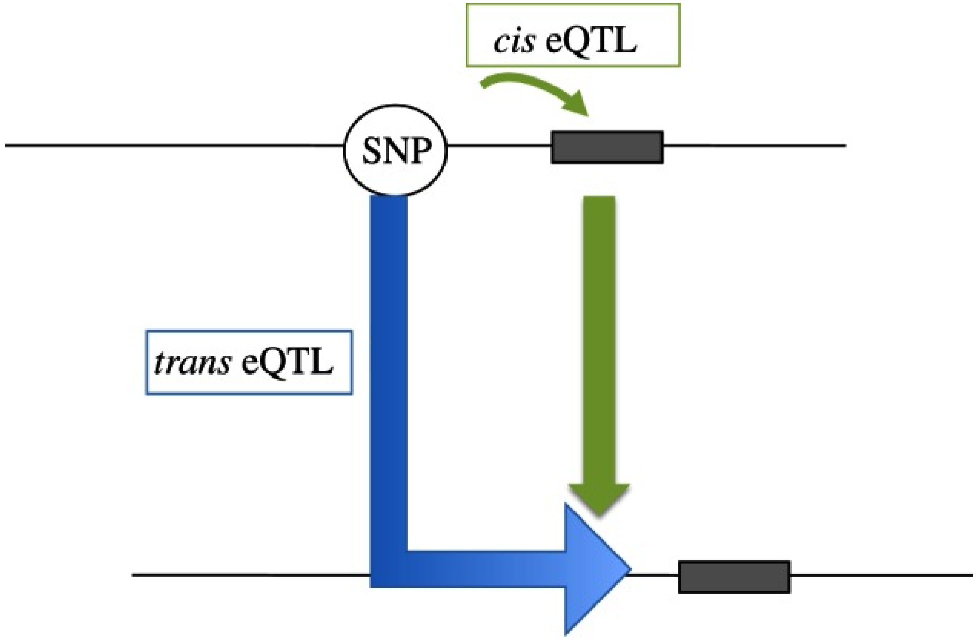
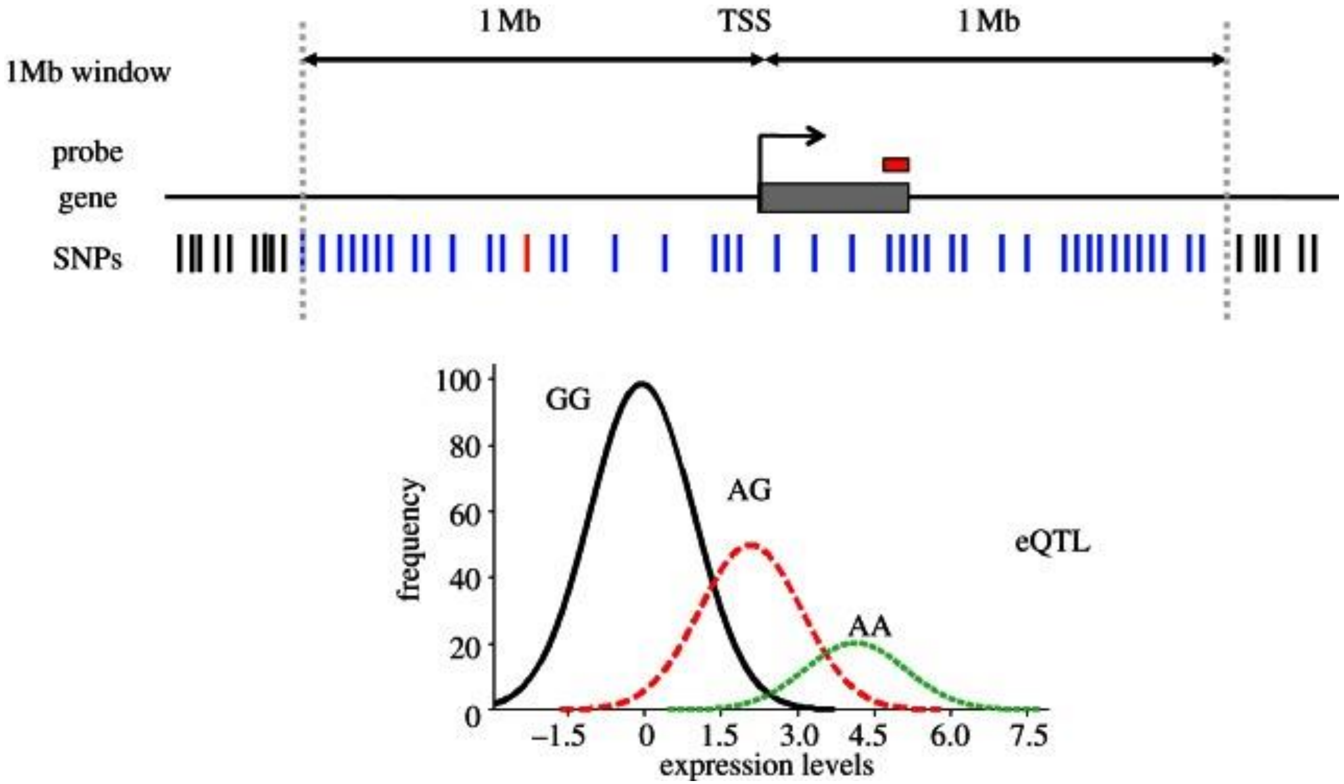
SNPs/AIMs as Expression Quantitative Trait Loci (eQTLs)

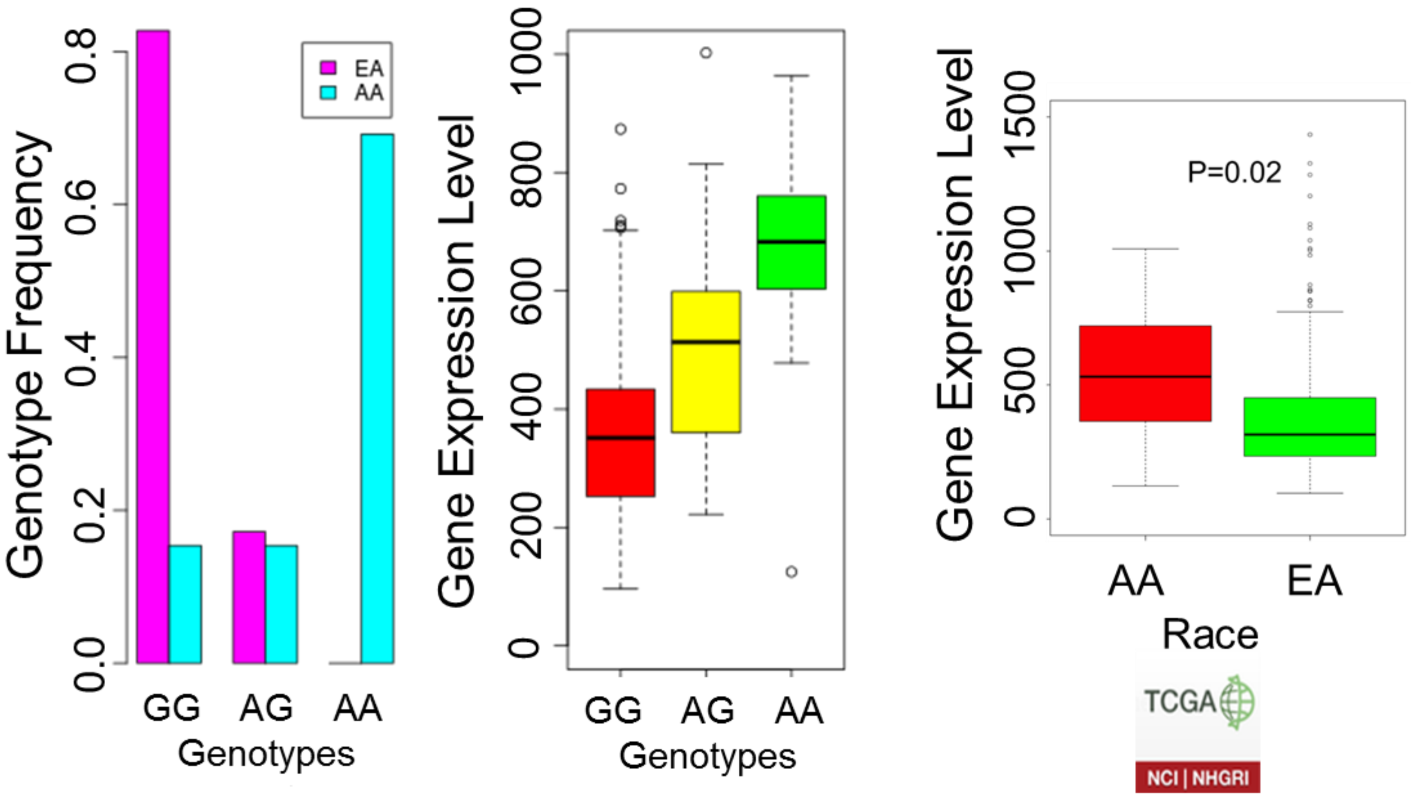




Nica and Dermitzakis, Philos Trans R Soc Lond B Biol Sci. 2013 Jun 19; 368(1620)

AIMs cis-eQTLs Influencing DNA Repair Genes

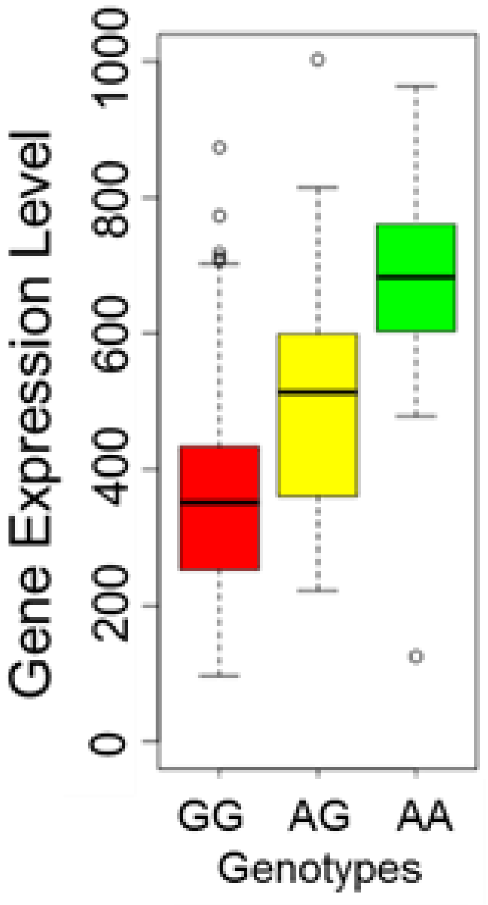
Example 2: effect of rs2272732 on *POLB* gene expression



- Frequency of ‘A’ is higher in Afr-Ams
- Allele ‘A’ is associated with higher expression of *POLB*
- Afr-Am HNC patients have higher level of *POLB* expression

Oral Cavity/Laryngeal Cancer Patients Treated with Radiotherapy/Platinum therapy

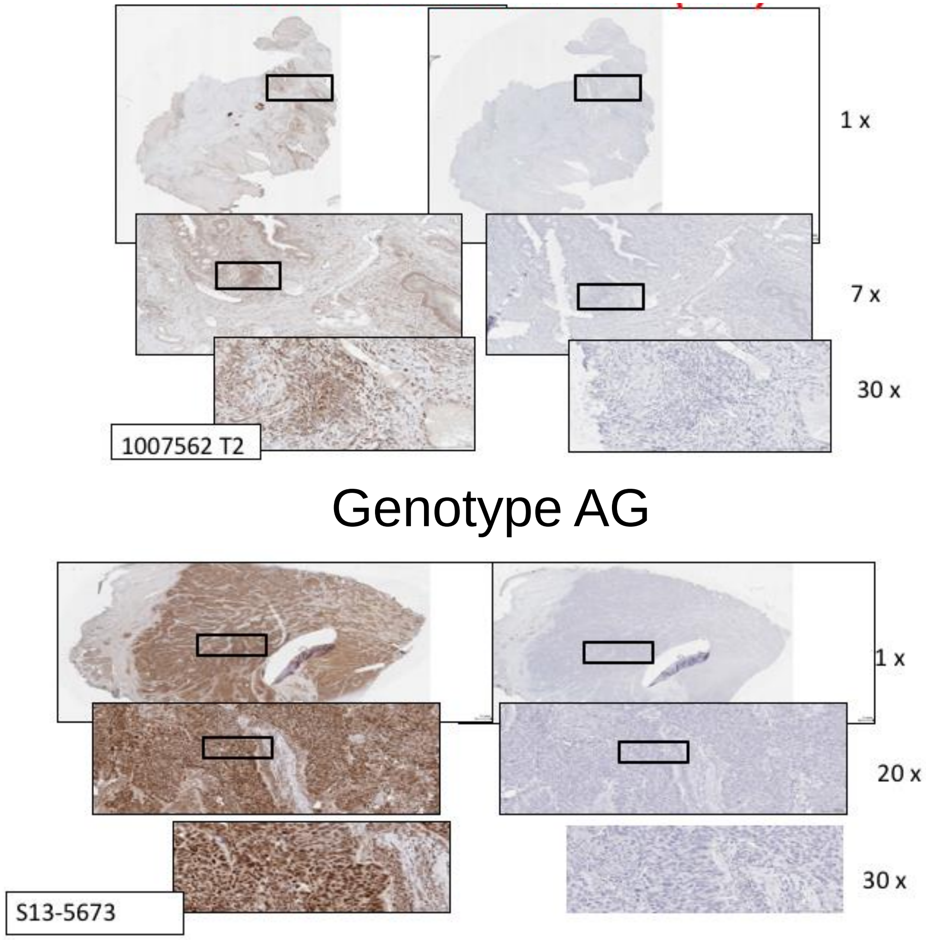
Ancestry-informative Single Nucleotide Polymorphism **rs227232** effects POLB gene expression



- African Americans more likely to have the AA or AG genotype
- AA/AG genotype associated with higher expression of DNA polymerase beta (*POLB*)

Genotype GG

Genotype AG



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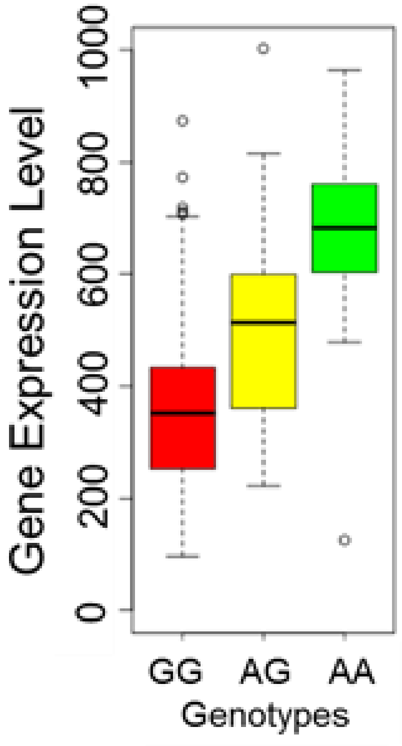
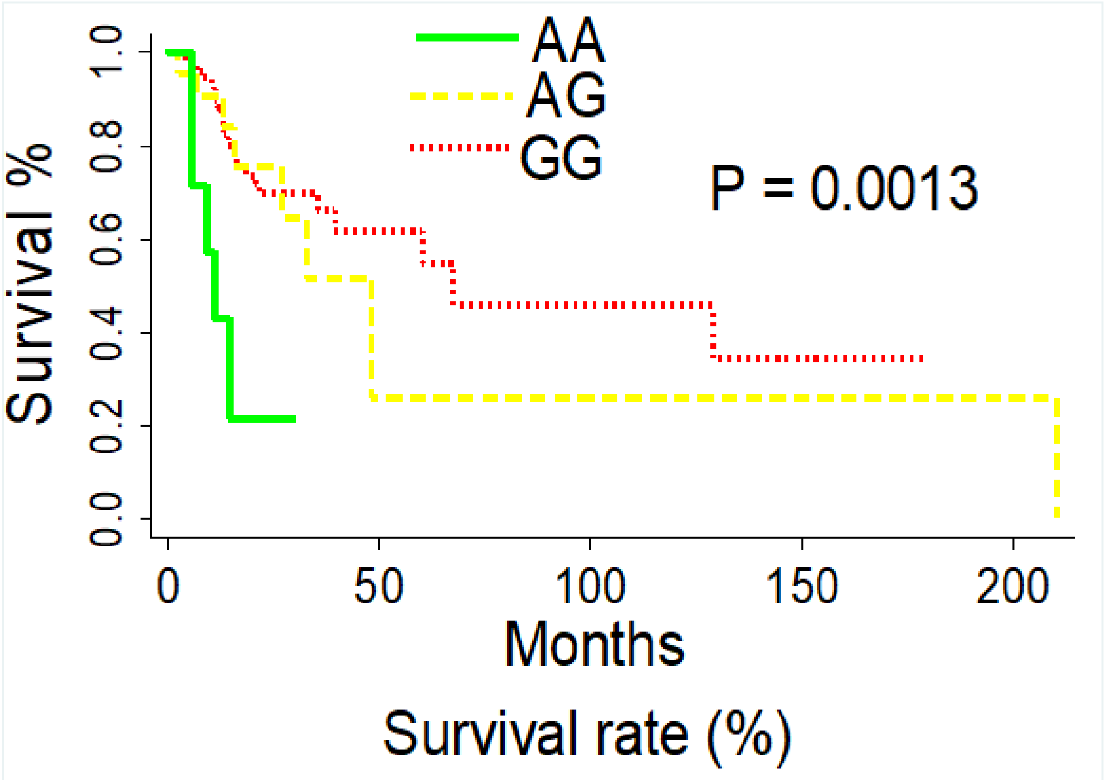
Oral Cavity/Laryngeal Cancer Patients Treated with Radiotherapy/Platinum therapy

Ancestry-informative Single Nucleotide Polymorphism **rs227232** effects POLB gene expression



- African Americans more likely to have the AA or AG genotype
- AA/AG genotype associated with higher expression of DNA polymerase beta (*POLB*)

Patients with the AA genotype have the lowest overall survival



Ramakodi et al, *Cancer*, 2017

Oral Cavity/Laryngeal Cancer Patients Treated with Radiotherapy/Platinum therapy

Global Genetic Ancestry and Risk of Death

Effect of African admixture on survival
in HNSCC patients with a history of platinum-based chemotherapy
and/or radiotherapy.

Risk of death (Overall):
8.99 (95% CI, 1.53-52.95; P = 0.015)

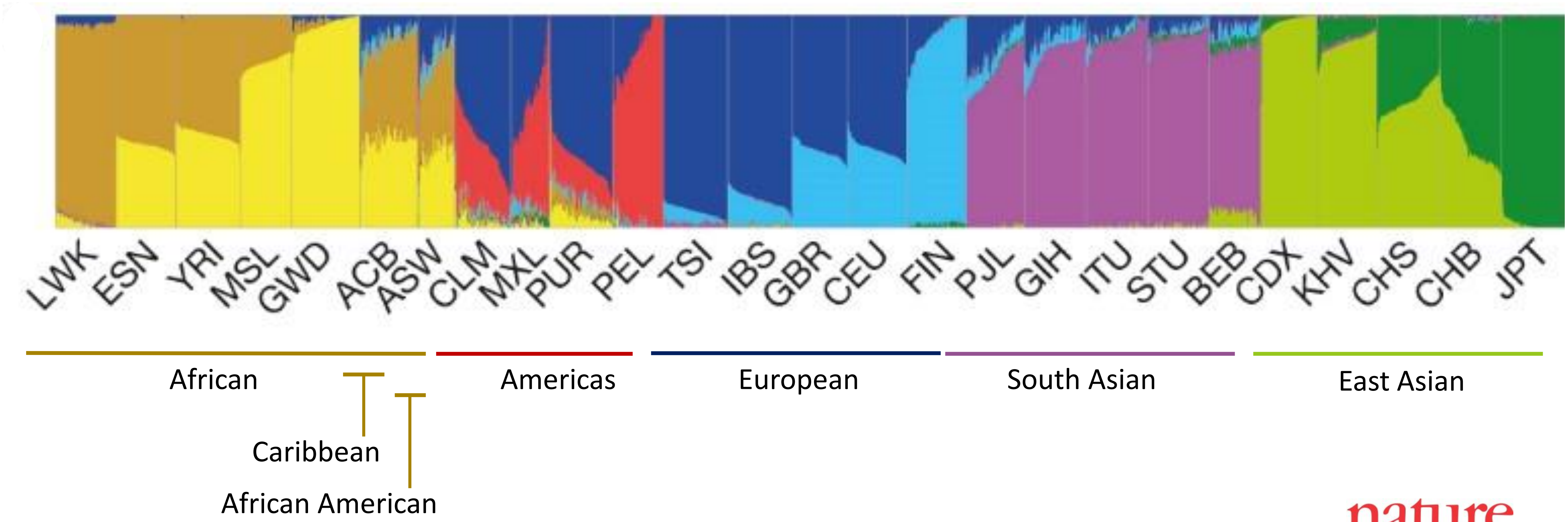
Risk of death (From disease):
7.12 (95% CI, 1.46-34.77, P = 0.015),

Markers of Genetic Diversity Around the World

SNPs that can define racial groups

Ancestry Informative Markers (AIMs)

Effect of genetic/genomic diversity will differ according to Populations/communities

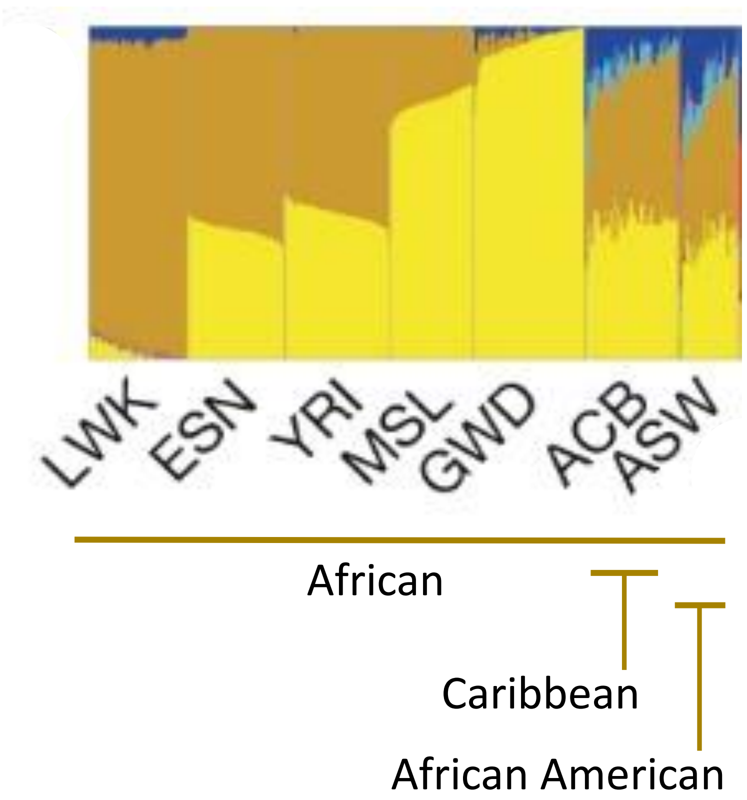


A Auton *et al*. *Nature* **526**, 68-74 (2015) doi:10.1038/nature15393

nature

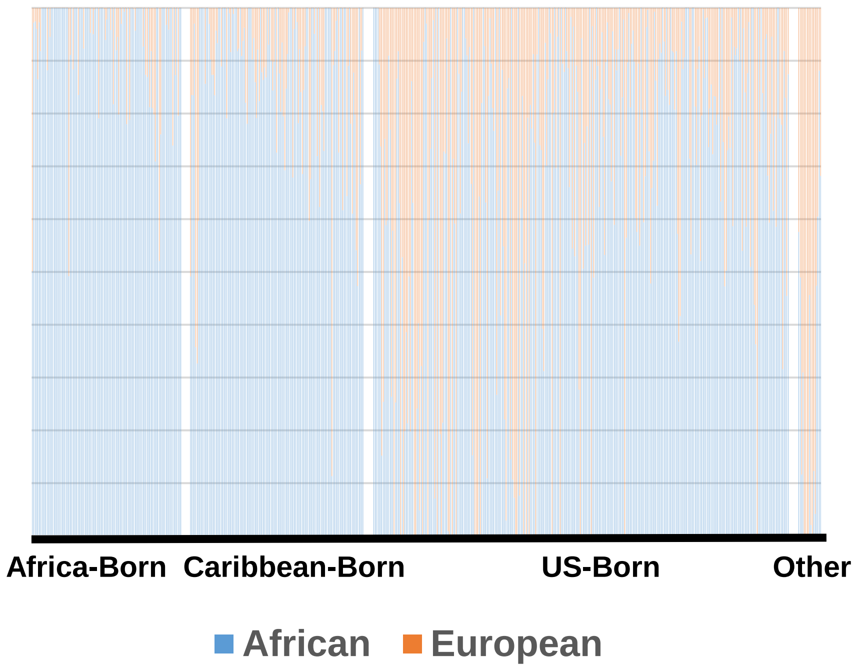
Markers of Genetic Diversity in Black Populations

Effect of genetic/genomic diversity may also differ within Communities



A Auton *et al*. *Nature* **526**, 68-74 (2015)
doi:10.1038/nature15393

Philadelphia
CAP3 Study
N = 573



Blackman, MPH, PhD(c); Ramakodi, PhD; Gibbs, BSc; Harlemon, PhD(c)

Genetic Diversity and Effects on Disease

Tremendous Effects

For some communities : Negative effects on disease

For other communities: Positive effects on disease

Review Questions

- **Q#1:** Can you describe how research that does not involve diverse communities might impact or influence health disparities?

- **Q#2:** The two lectures highlight that disease patterns (incidence and mortality), clinical presentation, and treatment response can vary dramatically by race/ethnicity and ancestral background. Can you provide some real world examples of the positive impact that diverse studies have made in helping to reduce health disparities? **Hint:** review *Oh et al. PLoS Med. 2015 Dec 15;12(12):e1001918.* PMID: 26671224