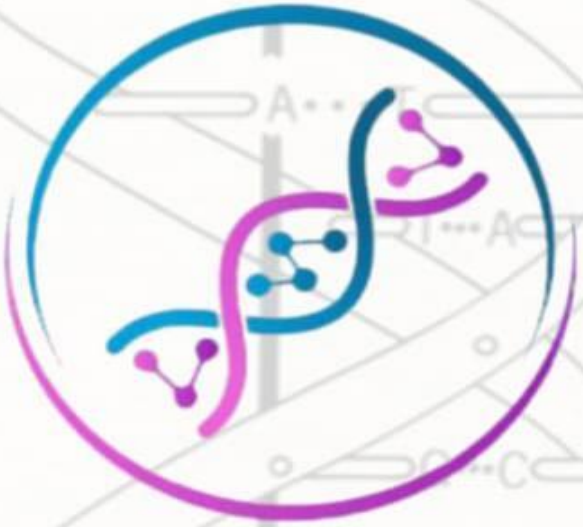
GENETIC VARIATION IN POPULATIONS



GENETIC VISION TEAM

- CCR5 : chemokine receptor type 5 .
- coreceptor present at the surface of immune cell (Macrophages) , which used by HIV to enter the cell, but sometimes mutation in the Co- receptor give a A new allele .
- this allele can't recognize by HIV which make the person resistant form HIV infection.

TABLE 9-1 Genotype Frequencies for the Wild-Type *CCR5* Allele and the Δ*CCR5* Deletion Allele

Genotype	Number of Individuals	Observed Genotype Frequency	Allele	Derived Allele Frequencies
CCR5/CCR5	647	0.821		
CCR5/ΔCCR5	134	0.168	*CCR5*	0.906
ΔCCR5/ΔCCR5	7	0.011	*ΔCCR5*	0.094
Total	788	1.000		

- look to this table , that illustrate the frequency of CCR5 and the mutant Δ CCR5 in certain population.

- CCR5/ CCR5 → homozygous (Wilde type)
- CCR5/ CCR5Δ → heterozygous
- CCR5Δ / CCR5Δ → homozygous mutant

- genotype frequency= number of individuals ÷ total

    - what is the frequency of CCR5/ CCR5?

= number of individuals have CCR/CCR5÷ total

= 647 ÷788 → 0.821

- what is the frequency of heterozygous?

134÷788 = 0.168

- allele frequency= 2× number of individuals÷ 2×total

- multiply by 2 because there are 2 allele

- what is the frequency of CCR5 ?

  - Homozygous CCR5/CCR5

  Each individual has two CCR5

  2×647= 1294

  - Heterozygous individual → CCR5/Δ CCR5
    Each individual has one CCR5 allele
    1×134= 134

    -Frequency of CCR5=(1294+134)÷ 2×(total).
    1428÷ 1578= 0.906

- What is frequency of Δ CCR5?
  1-0.906= 0.094

    - Or you can calculate it as we maintain above.

      Hardy- Weinberg law (equilibrium)
      Frequency of three genotypes AA,Aa,
      and aa is given by the term of binomial expansion.

      $(p+q)^2 = p^2 +2pq + q^2$

      P^2= AA
      2pq = Aa
      q^2 = aa

There are assumption for hardy- Weinberg law to become we can use it.

1- Large population: because there is flactuation in genome type frequency, if the population is small.

2- random matings : not assorting mating (no select

3- No mutation .

4- No selection: against phenotype and Exclud it from population.

5- No immigration: out or in population.

Application of hardy- Weinberg law with autosomal recessive disease

- PKU → Phenylketonuria: an autosomal recessive disease in which the patient has decreased metabolism of amino acid phenylalanine.

- PKU can lead to intellectual disability.

- frequency of PKU in given population 1 out of 4500 .
- because the PKU is autosomal recessive disease it must two mutant allele to express the disease.

$q^2 = 1 \div 4500$

$q = 0.015$

$p = 1 - 0\ 0.015 \rightarrow p = 0.985$

$2pq = 2 \times 0.985 \times 0.015 \approx 0.03$

Carrier frequency is 3%

Hardy- Weinberg equation with x-linked Phenotype

- color blindness : recessive x-linked disease in which a patient can't differentiate between color .

X* → normal allele (p)

X° → mutant allele (q)

In a given population the frequency of X* is 0.92 and the frequency of X° is 0.08 , calculate the frequency of genotypes for

1) Normal Homozygous
2) Normal heterozygous
3) Color blind

Because the males has only one X chromosome

One allele:

Normal color vision male , p= 0.92

Color blind male, q = 0.08

But, for female → like autosomal disease

$(p+q)^2 = p^2 + 2pq + q^2$

$P = 0.92$, $q = 0.08$

$P^2 = 0.8464$ → Homozygous normal (female)

$q^2 = 0.0064$ → color blind (female)

$2pq = 0.1472$ → heterozygous normal (female)

Normal combine female

= Normal Homozygous+ normal heterozygous

= 0.8464+ 0.1472 → 0.9936

TABLE 9-3 X-Linked Genes and Genotype Frequencies (Color Blindness)

Sex	Genotype	Phenotype	Incidence (Approximate)
Male	X^+	Normal color vision	$p = 0.92$
	X^{cb}	Color blind	$q = 0.08$
Female	X^+/X^+	Normal (homozygote)	$p^2 = (0.92)^2 = 0.8464$
	X^+/X^{cb}	Normal (heterozygote)	$2pq = 2(0.92)(0.08) = 0.1472$
		Normal (combined)	$p^2 + 2pq = 0.9936$
	X^{cb}/X^{cb}	Color blind	$q^2 = (0.08)^2 = 0.0064$

- **factors cause non random matings**

- Random matings: disrupt hardy- Weinberg equilibrium .

1- Startification : there are a class in population and each class individuals mating each other ” no mating ”

2- Assortative mating : similar people mating each other (taller– taller) , (blond- blond)

3- Consanguinity relatives mating.

- This three factors increase Homozygousity which lead to disruption of hardy- Weinberg equilibrium .

- Startification: the presence of sub groups Genetically separated.

- When the mating only from the same sub group this will increase the homozygous for certain allele, for example in certain population there is a sickle cell anemia, if there is a random mutation , the allele which cause a sickle cell anemia will distribute in population (diluted) but if there is mating only between individual in same sub group, this will lead to increased the homozygous genotype for allele that cause sickle cell anemia .

Summary : sickle cell anemia is autosomal recessive Disease , in order to express the disease two allele must be exist, if the mating occur only from the same sub group this will lead to increase Homozygous for the allele that cause the disease, but when the mating between individual in different sub groups this will decrease the likely for homozygous for the allele than cause the disease.

Hypotical situation

For autosomal recessive disease, in certain . population there two sub group.

1- Majority 90%
2- Minority 10%

• In the minority group the frequency of the allele That cause the disease “q” = 0.05 .
• the normal allele “p” = 0.95 .

• in the majority group, the frequency of the allele that cause the disease “q” ≈ 0 .
• approximately 0 because it too small

• in the majority group the frequency of the normal allele “p” ≈1 .

• in the case of random mating :

q (pop) : q (maj) × q(min) × (minority ÷ total)

- q(maj) ≈ 0 , it doesn’t involve in equation.
- Minority ÷ total → minority propertion .
  q(pop) = q(min) × (minority ÷ total)?
  = 0.05 × (10%÷100%)
  = 5× 10^-3

q^2 (pop) = 5×10^ -5 , frequency of disease in population.

• In the case if the mating only between individual in the minor sub group (mating exclusive within minority group)

q (min)= 0.05
q^2 (mim) = 2.5× 10^-4

In the case of mating between different sub group		in the case of mating only in same sub group
2.5 × 10^ -5	<	2.5 × 10^ -4

Conclusion:

The frequency of disease genotypes will increase if the mating occur between individual only in the same sub group.

In thisexample the disease frequency was increased 10 fold .

Assortative mating

• Choice of mate because mate possesses some particular trait .

• this Tend to be positive thus increasing proportion of homozygotes at the expense of heterozygotes.

• for example individual with AA mating together, and individual with aa , this will lead to decrease the frequency of heterozygous in population → which affect hardy- Weinberg law

For example achondroplasia (reduce bone growth) it's autosomal dominant disorder, usually the patient is heterozygous.

• But in the case of parents are both affected the child could be homozygous for mutation.

• both heterozygous and homozygous are affected by achondroplasia but homozygous of mutation is more sever and most of them die (lethal) .

• it’s very rare achondroplasia people mate with normal people, usually achondroplasia people mating together which lead to increase the homozygous in the population.

• if the male and female have recessive disease and mate , all of offspring will have a disease, except the disease show genetic heterogenity

Genetic heterogenity: mutation in different gene cause the same disease.

Example: deafness: loss of hearing

More than one gene control the hearing, mutation of any of these genes lead to deafness.

Assum two genes control the hearing gene A and gene B , for each gene if the person has two copies of mutation this lead to express the disease

AA bb → express the disease
aa BB → express the disease

AA bb × aa bb → AaBb → normal

If male and female have deafness but each has the mutation at different gene there is likely to get normal offsprings this is called genetic heterogenity.

But, If both have the mutation that cause the disease at the same gene all offspring will have the disease.
aaBB × aaBb → aaBB (effected)\ aaBb (effected).

•Consanguinity → increase the frequency of autosomal recessive disease in which carrier of disorder mate

• xeoderma pigmantosa : a rare autosomal recessive disease which result from mutation in protein that involve in excision repair system.

• 20% of exoderma pigmantosa cause due to consanguinity.

• genetic isolate : small population derived from a limited number of ancestors.

• Tay-Sachs is 100 fold more in Ashkenazi Jews.
• in general population : 1per 360000 has Tay-Sachs disease.
• in Ashkenazi Jews 1 per 3600 has Tay-Sachs disease.

- carrier frequency in general population 1 per 300

- carrier frequency in Ashkenazi Jews 1 per 30 .

- this because the Ashkenazi Jews mate together, so no diluted for defected allele, this increase the homozygous of disease.

- changes in allele frequency due to mutations or selection usually occur slowly in small increments and cause less deviation from hardy- Weinberg equilibrium.

- at least for recessive disorder .

- cofficent of selection (S) : Is the measure of loss fitness (f) , S= 1-f

• fitness: does the patient with specific disease or disorder can reach the reproductive age and transmit the mutation to next generation or die before.

• 1 fitness: the patient can transmit the mutation to next generation.

• 0 fitness: the patient can't reach reproductive age (die) to transmit the mutation to next generation.

• all the disease and disorder which are 0 fitness result from " De-novo mutation "

• some disease are between 0-1 fitness.

(S) is proportion of mutation allele that aren't passed to the next generation and lost as result of selection (opposite of fitness) .

• there is inverse relationship between selection and this allele.

mutation and selection balance in dominant disease.

• in selection: some allele will excluded from gene pool , new mutations composed the decrease by arising new allele.

• if there a selection in certain pool and loss genes from gene pool there is new mutation.

M= sq

M : mutation
S : co- efficient of selection
q: allele frequency

Q- if s= 1 what does that mean?

S= 1- f
1=1-f
F= 0 → all patients have this mutation can't reach a reproductive age to transmit to next generation, also they were geten " Denovo mutation " new mutation.

• equation

M = q , what does that mean?

All individual have this allele were geten from new mutation .

For x-linked disease

Usually selection for males , because female have two x chromosome .

• M = s (q÷3) , selection occur at ⅓ of alleles

Male has 1 allele where female has 2
total = 3

Male= ⅓ alleles

Genetic drift: Random fluctuation of Allele frequencies in small Population, Chance event can have much eftet greater Effect on Allele frequencies in small population than large population.

Founder effect

⇨ Special form of Genetic Drift

Who induce the ffect

• for example , specfic Disease found in france Presed in low frequener, if a group of Pepole 10 for example
3 out 10 has a certain disease and this group migrute to another Contry and etublish a population in small vallige after time the frequoner of disease is increased , and if we

comparethe disease frequency in two population we found the disease frequency is greater in small vallige .

Supposed france contain 10000000 individuals ,10000 individuals have the disease .

Where the small vallige contain 1000 people 300 have the disease.

In France → (10000÷10000000) × 100%
= 0.1% of population people have the disease
In vallige → (300÷1000) ×100%
= 30% of population have disease.

Gene flow

Gradul diffusion of genes from on Population to another across barrier (Physical or cultural).

Migration

In is Jordan there is specfic Alleles frequencie peoples come from Europe, America and Asia and live in Jordan these Pepoles have new Alleles that aren’t found in Jordan and these allele now introduced into Jordan population (physical barrier)

• when the people from different culture, each culture could be contain specific traits (allele) .

• Genetic admixture: genes of migrant population
With their own Chracterstic allele frequencies are gradually mergea into gene Pool of the population into which they have migrated .

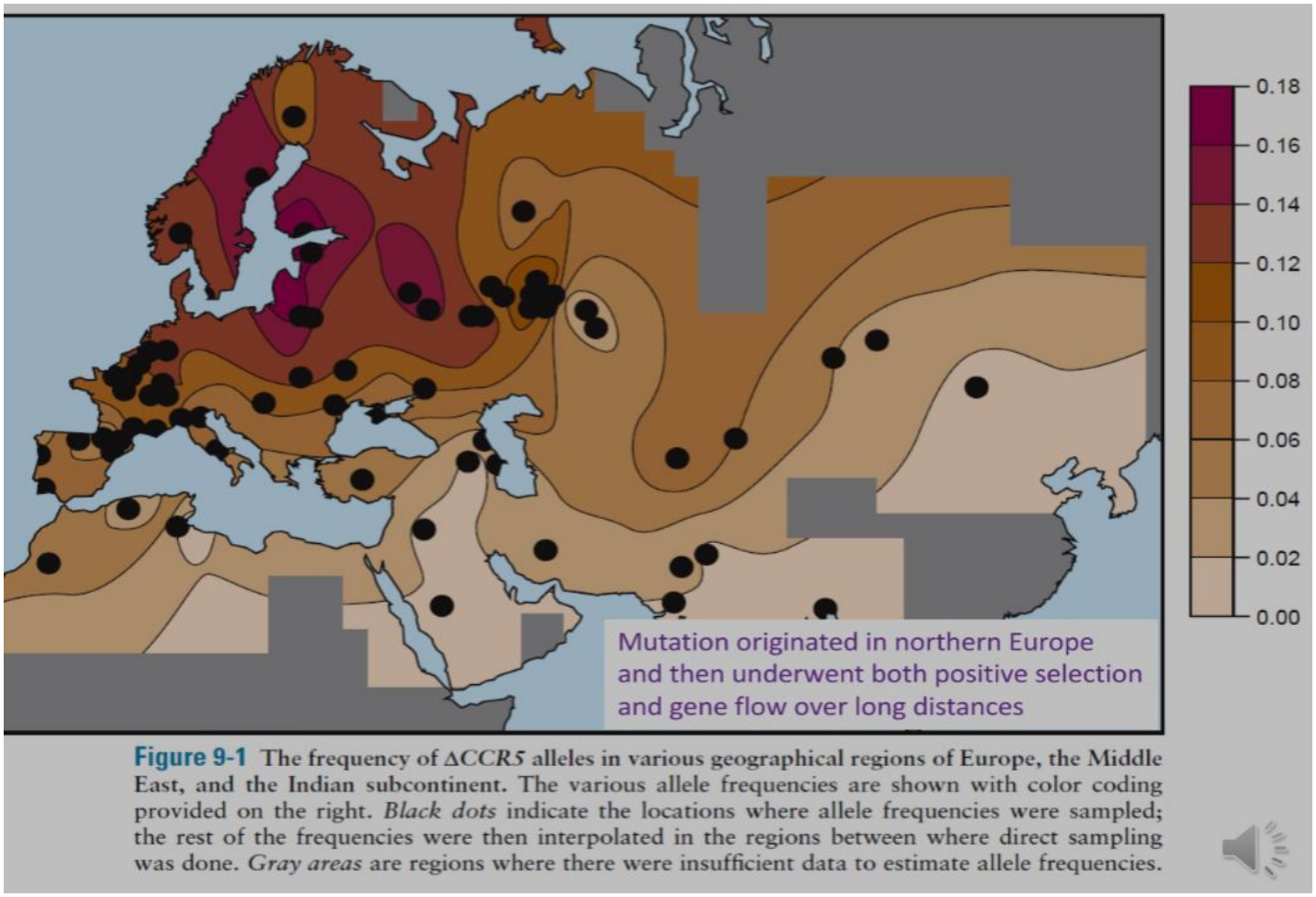


Figure 9-1 The frequency of Δ*CCR5* alleles in various geographical regions of Europe, the Middle East, and the Indian subcontinent. The various allele frequencies are shown with color coding provided on the right. *Black dots* indicate the locations where allele frequencies were sampled; the rest of the frequencies were then interpolated in the regions between where direct sampling was done. *Gray areas* are regions where there were insufficient data to estimate allele frequencies.

The frequency of ΔCCR5

ΔCCR5 is concentrated in northern Europe , black Dots indicate regions where the analysis for ΔCCR5 frequeney occur this grap show ΔCCR5 frequency in different geographical areas, as we notice an increase and decrease in Δ CCR5 frequency .

• the frequency increased in northern Europe and Sturt to Decrease whenwe move from southren Europe to another Countries this is beacuse of migration.

• So mutution originated in Nothern Europe and then underwert Positive selectin (this Mutation Protect Pepole from HIV and some other viruses) by prevent the HIV enter the immune cells.

• Ethnic differences in the frequency of Genetic diseas .

⇒ different mutations in the Population are differ from Population to another

The Percentage of mutations in certain country it not necessary the same in other countries.

TABLE 9-5 Incidence, Gene Frequency, and Heterozygote Frequency for Selected Autosomal Disorders in Different Populations

Disorder	Population	Incidence	Allele Frequency	Heterozygote Frequency
Recessive		q^2	q	$2pq$
Sickle cell anemia (*S/S* genotype)	U.S. African American	1 in 400	0.05	1 in 11
	Hispanic American	1 in 40,000	0.005	1 in 101
Rh (all Rh-negative alleles)	U.S. white	1 in 6	0.41	≈1 in 2
	U.S. African Americans	1 in 14	0.26	≈2 in 5
	Japanese	1 in 200	0.071	≈1 in 8
Phenylketonuria (all mutant alleles)	Scotland	1 in 5300	0.014	1 in 37
	Finland	1 in 200,000	0.002	1 in 250
	Japan	1 in 109,000	0.003	1 in 166
Dominant		$2pq + q^2$	q	
Familial hypercholesterolemia	Isolate in Quebec, Canada	1 in 122	0.004	—
	Afrikaner, South Africa	1 in 70	0.007	—
	U.S. population	1 in 500	0.001	—
Myotonic dystrophy	Isolate in Quebec, Canada	1 in 475	0.0011	—
	Europe	1 in 25,000	0.00002	—

Hemolytic disease (RH disease)

For example Incidence of RH negative in U.S white 1 in 6 but in African American 1 in 14.

, For Japanese 1in 200 .

Hemolytic disease of newborn caused by Rh incompatibility .

If the father Rh+ , Rh- and the mother Rh-,Rh-

The offspring:
Rh+, Rh- (positive Rh)
Or
Rh-, Rh- (negative Rh)

Embryo could has **RH+** and mother **Rh**- Pregnant woman inject by RH immune globulin at 28-32 gestation and again after pregnancy to clear any
Rh – Positive fetal cells from mother circulation before she sensitized and Produce Anti-Rit which
Could be her side effect of second child if he has RH+ .

Founder effect

A persons have mutation come to small Population and then start l increasing the incidence of disease .

Positive selection for heterozygous there is advantage in the presence of Heterozygous for Specsic Allele and this lead to continuity of Allele existence in population and sometimes it is better than Homozygous natural Allele .

• blanced Polymorphism: situation in which selective forces aganist Allele and forces with the Allele.

• sickle cell disease : recessive disease
Dangerous disease

• Malarin: Is dangerous disease, which kill .

- Popole without sickel cell anemia (have both normal Alleles) die by Medarin .

For heterozygous : has one normal allele one mutant allele (Normal person) :

Plasmodium can't enter RBC for peole who have one Mutant Allele, mutation protect the person from malaria and also also the normal Allele will contine exist in Population .

- so this advantage make this allele still exist in population .

- **Genetics aut ancestry**

AA →African American

EA→European American

HA→ Hispanic American

430 individuals were performed Ancestory Marker test , the majority of them have Africa markers .

• Most of Europion white are originated from Europe because they have Europe markers.

• Hispanic are genetically heterozygous with ancestors from many parts of world .

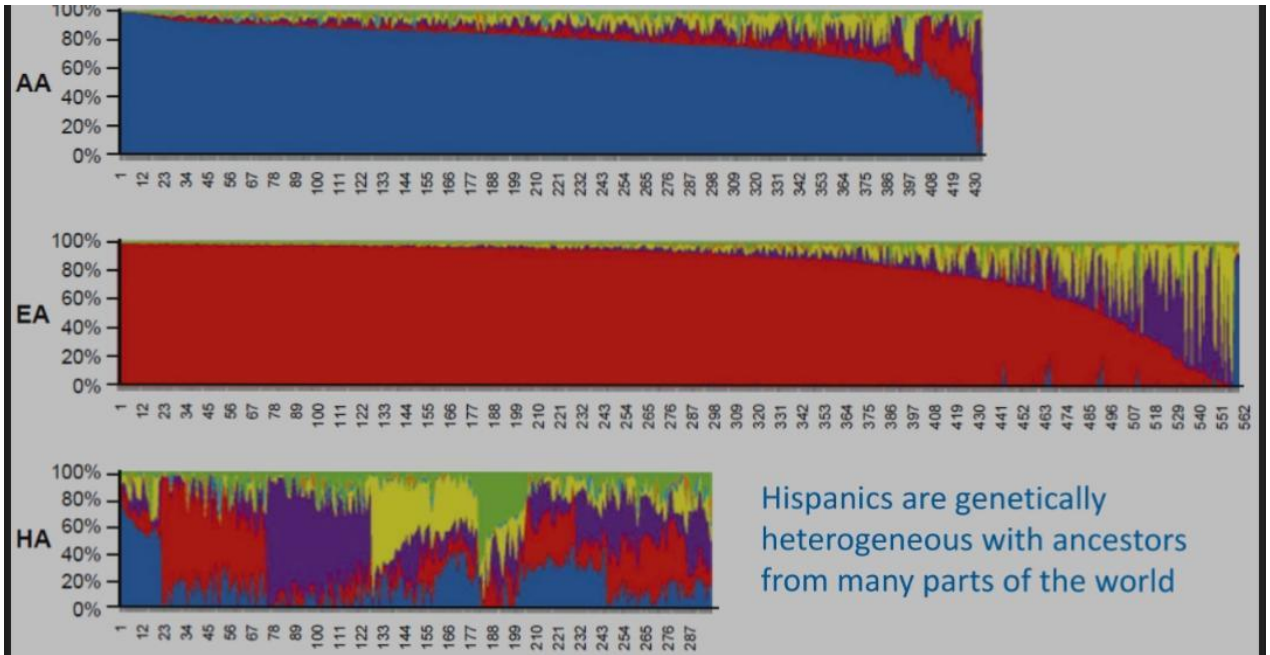


Figure 9-2 Mixed ancestry of a group of Americans who self-identify as African American (AA), European American (EA), and Hispanic American (HA) using ancestry informative markers. Each vertical line represents one individual ((totaling hundreds, as shown by the numbers), and subjects are displayed according to the predominant ancestry contribution to their genomes. Different colors indicate origin from a different geographical origin, as inferred from AIMs, as follows: Africa (*blue*), Europe (*red*), Middle East (*purple*), Central Asia (*yellow*), Far East Asia (*cyan*), Oceania (*amber*), and America (*green*). Most African Americans have genomes of predominantly African origin (*blue*), and most European Americans have genomes of predominantly European origin (*red*), although there is a range of ancestry contribution among different subjects. In contrast, Hispanic Americans are a more heterogeneous group, and most individuals have genomes with significant contributions from four or five different origins. *See Sources & Acknowledgments.*

• Ancestral contribution

• Puerto Rican peoples are genetically heterozygous , the majority of them europine and small proportion from a West African and almost no Native American ancestors.

conclusion: There is no controbution from American ancestral to Puerto Rican people.

• Three dimensional way Analysing data so that you can conclude or you can determine the Ancestry of the Population .

Race its Real or fiction ?

It could have some sides relered to genetic
its not only the color of hair or skin also Religen and culture .

• its good to know the Race which Could help in diagnosis.

• African : high risk of sickle cell anemia .
• whites : high risk of cystic fibrosis.

• Alskuazi jaws: risk of Tay - Sach disease.

But in future → new techniques will develop to analysis the specific Alleles to know the risk to get some specific disease or not depending on Alleles them selfs more than looking at the intended or other characterized might be used in a different ways that its intended .

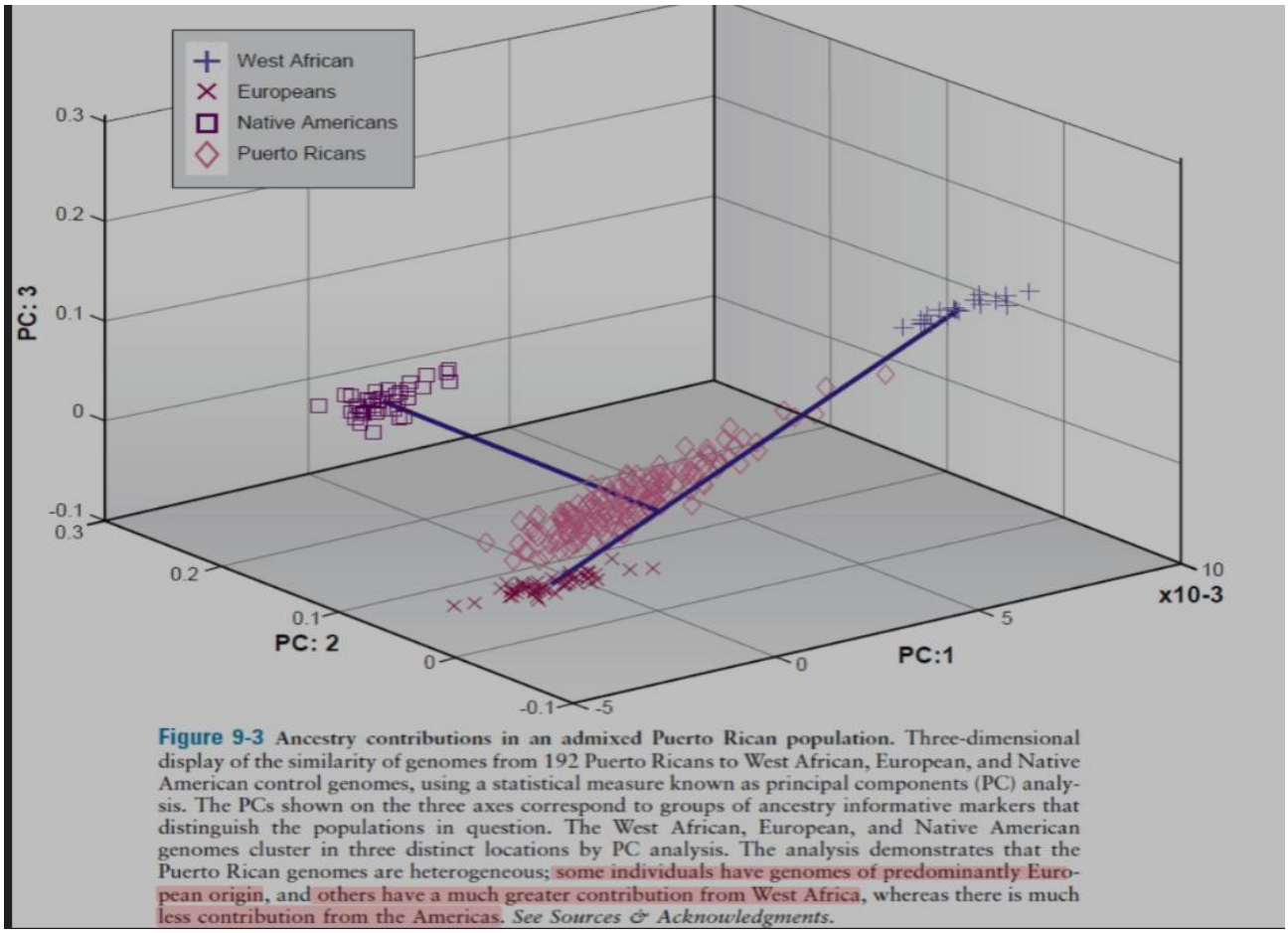


Figure 9-3 Ancestry contributions in an admixed Puerto Rican population. Three-dimensional display of the similarity of genomes from 192 Puerto Ricans to West African, European, and Native American control genomes, using a statistical measure known as principal components (PC) analysis. The PCs shown on the three axes correspond to groups of ancestry informative markers that distinguish the populations in question. The West African, European, and Native American genomes cluster in three distinct locations by PC analysis. The analysis demonstrates that the Puerto Rican genomes are heterogeneous; some individuals have genomes of predominantly European origin, and others have a much greater contribution from West Africa, whereas there is much less contribution from the Americas. *See Sources & Acknowledgments.*

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