The Distribution of Human Differences

Expansion Routes of Homo sapiens

If all this genetic variation is so recent and continuous, why do we think of it in categorical terms?

The European Case in More Detail

Population movements and population structure since the first Homo sapiens also affects genes

European Y-chromosome Haplogroups

- Seven haplogroups account for over 90% of Y-chromosome lineages in Europe today
- Early lineages
  - R1b (30 kya)
  - I1a and I1b (20 kya)
- Neolithic lineages (~10 kya)
  - J2 and E3b probably spread with agriculture
  - R1a appears to be consistent with Indo-European language spread on horseback
- More recent (~3 kya)
  - N coming from Siberia with reindeer herders
Y-chromosome Haplogroup R1b
- This is the earliest expansion into Europe, 30 to 40 kya
- Comes from Central Asia M45 via M173

Y-chromosome Haplogroup I1a
- Refuge in Iberian Penninsula ~20 kya
- Comes from Middle East M89 via M170

Y-chromosome Haplogroup I1b
- Appears in the Balkans ~15 kya
- One additional marker to I1a

European Refugia LGM

Y-chromosome Haplogroup J2
- J Haplogroup originates ~15 kya in the Fertile Crescent
- J2 Spreads with early farming

Map of the distribution of the earliest archaeological sites in Europe and the Middle East showing evidence of agriculture
Y-chromosome Haplogroup E3b
- Appears ~20 kya in the Middle East
- Spreads with farming to South and Eastern Europe

Y-chromosome Haplogroup R1a1
- Appears ~10 – 15 kya in Southeastern Europe
- Horse borne, possibly spread of proto-Indo-European

Y-chromosome Haplogroup N
- From Siberia ~10 kya dispersed with reindeer herding and the Uralic languages over the past ~3 - 4 ky

mtDNA Haplogroup U
- Mutation occurs ~50 kya
- Earliest mtDNA line in Europe, ~30 – 40 kya

mtDNA Haplogroup V
- Appears ~15 kya
- Likely spread from Iberian glacial refuge

mtDNA Haplogroup H
- Gets to Europe ~30 kya but spreads widely after last glaciation
- Most common in Europe today
mtDNA Haplogroup T

- Appears ~40 kya, but thought to have spread with agriculture

mtDNA Haplogroup K

- Appears ~20 kya and moved northward out of the Near East
- High frequencies in Ashkenazi Jewish populations

mtDNA Haplogroup J

- First appears ~40 kya in the Indus Valley region
- Major signature of the expansion of agriculture

Is this an on-going process?

Admixture in African Americans in South Carolina

- Average European Admixture: 3.5%
- Low Country: 11.8%
- Columbia: 17.7%

What else accounts for the distribution of genetic variability?

- Mutation
- Genetic Drift
  - Small, isolated populations
  - Founder effect
    - Accounts for some aspects of ABO blood group distribution
- Natural Selection
  - Accounts for many characteristics like skin color (next week) and sickle cell hemoglobin
Distribution of the A allele

Causes of Distribution of ABO

- Genetic Drift
  - Isolation of small populations allows for the build up of random changes in gene frequencies
  - These random effects probably account for some of the peculiarities in the distribution of the ABO alleles
    - The 100% frequency of O in some Native South American groups
    - The 50+% frequency of A in Australian and Native American populations

The Native American Case

- MtDNA analysis in 2005 suggested that the number of breeding founders of Native Americans may have been as few as 80-300 individuals
  - Genetic drift would have been very influential in such a population
    - Both classic drift and founder effect
    - Founders: near zero B, low A, O most frequent

Sickle Cell

- Mutation of thymine nucleotide to an adenine nucleotide
  - Causes substitution of valine for glutamic acid at the 6th position of the β chain
- Three genotypes, three phenotypes
  - AA Homozygous Normal; “Normal”
  - AS Heterozygote; “Sickle Cell Trait”
  - SS Homozygous sickle; “Sickle Cell Anemia”

Symptoms of Sickle Cell Anemia

- As a result of sickling and the premature aging of red blood cells from sickling, there are fewer than normal red blood cells, the general condition referred to as anemia
- There is an increased risk of severe infections, especially bacterial infections—such as sepsis (a blood stream infection), meningitis, and pneumonia, especially in early childhood
  - The risk of infection is increased because the spleen does not function normally
Symptoms of Sickle Cell Anemia

- **Splenic sequestration crisis:**
  - The spleen is the organ that filters blood
  - In children with sickle cell disease, the spleen can enlarge rapidly from trapped red blood cells creating a situation that can be life-threatening.

- **Stroke:**
  - This happens when blood vessels in the brain are blocked by sickled red blood cells
  - Signs include seizure, weakness of the arms and legs, speech problems, and loss of consciousness.

Symptoms of Sickle Cell Anemia

- Children with sickle cell anemia experience slowed growth and delayed maturation, including puberty as a result of the anemia and infections.
- There are repeated, painful episodes, called vaso-occlusive crises, associated with blockages of the circulatory system
  - Frequently seen as swelling of extremities
- There is a progressive degeneration of organs from impaired circulation
  - *Without medical care this is frequently lethal at an early age!*

Swollen Hands from Sickling

The Malaria Cycle of Infection

- **Mosquito bites an uninfected person**
- **Sporozoite incubates in Liver Cells 5 - 10 days**, metamorphosizes to merozoite
- **Merozoite infects Red Blood Cells**
- **Host immune response causes Plasmodium to sexually differentiate**
- **Mosquito bites infected person**
- **Plasmodium changes to sporozoite in intestine, migrates to salivary glands**

Epidemiological Correlations

- A comparison of *Plasmodium falciparum* parasites in blood samples from children of SS and AS genotypes in Nigeria to that of children with AA genotypes showed:
  - SS and AS children had lower frequencies and lower densities of parasites than AA children (lower levels of malaria infection)
  - Fertility did not differ between AA and AS, but 29% more AS individuals survived to adulthood (selection based on survival of malaria, not increased fertility of heterozygotes)
Biochemical studies

- The interaction of the *Plasmodium* parasite and sickle cell hemoglobin takes place in the red blood cell
- *Plasmodium* metabolism causes sickle cell hemoglobin to form the fibers that results in sickling
- The development of *Plasmodium* is disrupted by sickling of the red blood cells
- Life cycle of parasite is cut short before it can cause the most severe symptoms

Heterozygote Advantage

- Best genotype to have where malaria is a severe threat to life is heterozygous (AS)
  - Heterozygotes are protected from malaria but don’t suffer severe symptoms of sickle cell
  - Homozygous normal (AA) individuals are more likely to die from malaria than heterozygotes (AS) or homozygous sicklers (SS)
  - Homozygous sicklers (SS) are much more likely to die from sickle cell anemia than heterozygotes (AS) or homozygous normals (AA)

Relative Fitness

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<th>AA</th>
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<th>SS</th>
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<td>0.80</td>
<td>1.00</td>
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Likelihood of surviving and reproducing compared to AS = 1

Deaths vs. Sickle Cell Frequency

- Deaths due to malaria
- Deaths due to sickle cell anemia

Five Haplotypes

| Haplotype | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 |
|-----------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Senegal   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Western   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Eastern   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cameroon  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Asian     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
Malaria has been a strong selector

- In addition to sickle cell hemoglobin, there are several variants like Hb\textsuperscript{C} and Hb\textsuperscript{D} and control region variants like the \( \alpha \) and \( \beta \) thalassemias
- Glucose 6-Phosphate Dehydrogenase deficiency is a red blood cell enzyme that has variants that reduce the severity of malaria