Population genetics

CH Chen
Population genetics

- **Population** = group of organisms of the same species living in the same geographical area

- **Population genetics** is the study of the distribution of genes in populations and of the factors that maintain or change the frequency of genes and genotypes from generation to generation.
Human Population genetics

Hardy-Weinberg Equilibrium

Factors affecting H-W Equilibrium
Law of Genetic Equilibrium

Hardy-Weinberg law

Hardy GH

Weinberg W
Hardy-Weinberg Equilibrium - important concepts

• **Allele frequency**: the proportion of a specific allele at a given locus, considering that the population may contain from one to many alleles at that locus.

• **Genotype frequency**: the proportion of a specific genotype at a given locus, considering that many different genotypes may be possible.

• **Phenotype frequency**: the proportion of individuals in a population that exhibit a given phenotype.
Hardy-Weinberg Equilibrium - allele frequency

1. two alleles at a gene - A and a
2. frequency of the A allele = p
3. frequency of the a allele = q
4. p + q = 1

\[
f_A = \frac{A}{A + a} \quad \text{(p)}
\]
\[
f_a = \frac{a}{A + a} \quad \text{(q)}
\]
\[p + q = 1\]
More than two alleles at a gene

1. Let $p$ = the frequency of the $A$ allele
2. Let $q$ = the frequency of the $B$ allele,
3. Let $r$ = the frequency of the $i$ allele.
4. $p + q + r = 1$

$$f_i^A = \frac{i}{|A| + |B| + i} \quad (p) \quad f_i^B = \frac{i}{|A| + |B| + i} \quad (q)$$

$$f_i = \frac{i}{|A| + |B| + i} \quad (r) \quad p+q+r=1$$
Law of Genetic Equilibrium

Hardy-Weinberg law

**Assumptions**

- Large population
- Random mating
- No natural selection
- No mutation
- No migration

If assumptions are met, population will be in genetic equilibrium.
Law of Genetic Equilibrium

Hardy-Weinberg law

- Allele frequencies do not change over generations.
- Genotypic frequencies will remain in the following proportions:

\[
\begin{align*}
 p + q &= 1 \\
p^2 + 2pq + q^2 &= 1
\end{align*}
\]

- \( p^2 \): frequency of AA
- \( 2pq \): frequency of Aa
- \( q^2 \): frequency of aa
Hardy–Weinberg principle

• the frequencies of alleles (variations in a gene) will remain constant in the absence of selection, mutation, migration and genetic drift.

• A second component of the Hardy–Weinberg principle concerns the effects of a single generation of random mating. In this case, the genotype frequencies can be predicted from the allele frequencies.
In a population study, 10000 individuals were genotyped for A locus. There were 5000 AA individuals, 2000 Aa individuals, and 3000 aa individuals. Is this population in Hardy-Weinberg equilibrium?

(1) \( f_{AA} = 0.5, f_{Aa} = 0.2, f_{aa} = 0.3 \)
    
    allele A frequency: \( p = 0.5 + \frac{1}{2} \times 0.2 = 0.6 \),
    
    allele a frequency: \( q = 0.3 + \frac{1}{2} \times 0.2 = 0.4 \)

(2) If this population were at Hardy-Weinberg equilibrium, one would predict that

\[ f_{AA} = 0.6^2 = 0.36, \quad f_{Aa} = 2 \times 0.6 \times 0.4 = 0.48, \quad f_{aa} = 0.4^2 = 0.16. \]

It is quite different than the observation. Thus the population is not at Hardy-Weinberg equilibrium.
After one generation with random mating, the population is at Hardy-Weinberg equilibrium.
Law of Genetic Equilibrium

Hardy-Weinberg law

Explains how Mendelian segregation influences allelic and genotypic frequencies in a population.
Hardy-Weinberg Equilibrium
- application

- Application of Hardy-Weinberg Equilibrium
- Determine allele frequency in a population
- Determine inheritance pattern
- **Determine allele frequency**
  - **Autosomal recessive diseases**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype frequency</td>
<td>( p^2 )</td>
<td>( 2pq )</td>
<td>( q^2 )</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Unaffected</td>
<td>F(_u)</td>
<td>affected</td>
</tr>
</tbody>
</table>

- **Disease allele frequency** \( q = (F_a)^{1/2} \)
  
  e.g. disease frequency \( (F_a) = 1/10000 \)
  
  disease allele frequency = 1/100
  
  carrier frequency = \( 2pq = 2 \times 0.01 \times 0.99 = 0.0198 \)
Determine allele frequency
- Codominant alleles

MN blood group: In a population, there were 233 type M individuals, 485 type MN individuals, and 129 type N individuals.

- $I^M$ allele frequency$= \frac{(233 \times 2 + 485)}{[2 \times (233 + 485 + 129)]} = 0.57$

- $I^N$ allele frequency$= \frac{(129 \times 2 + 485)}{[2 \times (233 + 485 + 129)]} = 0.43 \quad = 1 - I^M$
- Determine allele frequency
  - **Multiple alleles**
    ABO blood group: type A=41.72%; type B=8.56%; type O=46.68%; type AB=3.04%
    - $I^A$ allele frequency = $p$;
    - $I^B$ allele frequency = $q$
    - $i$ allele frequency = $r$

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Type A</th>
<th>Type B</th>
<th>Type AB</th>
<th>Type O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>$I^AI^A, I^Ai$</td>
<td>$I^BI^B, I^Bi$</td>
<td>$I^AI^B$</td>
<td>ii</td>
</tr>
<tr>
<td>Genotype frequency</td>
<td>$p^2+2pr$</td>
<td>$q^2+2qr$</td>
<td>2pq</td>
<td>$r^2$</td>
</tr>
</tbody>
</table>

\[
r=(O)^{1/2}= (0.4668)^{1/2}=0.683
\]
\[
A+O= p^2+2pr+r^2=(p+r)^2=(1-q)^2
\]
\[
q=1-(A+O)^{1/2} =1-(0.4172+0.4668)^{1/2}=0.06
\]
\[
p=1-(B+O)^{1/2} =1-(0.0856+0.4668)^{1/2}=0.257
\]
- Determine allele frequency
  - X-linked recessive disease

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Unaffected</th>
<th>Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>(X^AX^A)</td>
<td>(X^AX^a)</td>
</tr>
<tr>
<td>Genotype frequency</td>
<td>(p^2)</td>
<td>(2pq)</td>
</tr>
</tbody>
</table>

Disease allele frequency \((q)\) = disease frequency in male

or

Disease allele frequency \((q)\) = \((\text{disease frequency in female})^{1/2}\)

Example - Color blindness:
  
  disease frequency is 7\% in male, 0.49\% in female

  Disease allele frequency = 7\%
Determine inheritance pattern

- Example - high myopia population study
- Disease frequency: 0.724%
- In the families with one affected parent, there were 104 offspring, of which 8 affected, frequency was 7.69%;
- In the families with unaffected parents, there were 1637 offspring, of which 10 affected, frequency was 0.61%.
- Based on these results, please determine inheritance pattern of high myopia in the population.
Determine inheritance pattern

Suppose high myopia in the population was inherited in AR

Disease allele frequency \((q) = (0.724\%)^{1/2} = 0.085\)

For the families with one affected parent

<table>
<thead>
<tr>
<th>Mating type</th>
<th>Frequency</th>
<th>Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA X aa</td>
<td>2p^2q^2</td>
<td>2p^2q^2</td>
</tr>
<tr>
<td>Aa X aa</td>
<td>2 \times 2pq \times q^2 = 4pq^3</td>
<td>2pq^3 2pq^3</td>
</tr>
</tbody>
</table>

Expected disease frequency in these families
\[= \frac{2pq^3}{(2p^2q^2 + 4pq^3)} = q/(p + 2q) = q/(1 + q) = 0.085/(1 + 0.085) = 7.83\%\]

Observed disease frequency in these families was 7.69\%, which is close to 7.83\%.
### Determine inheritance pattern

For the families with unaffected parent

<table>
<thead>
<tr>
<th>Mating type</th>
<th>frequency</th>
<th>Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA X AA</td>
<td>p^4</td>
<td>p^4</td>
</tr>
<tr>
<td>AA X Aa</td>
<td>4p^3q</td>
<td>2p^3q</td>
</tr>
<tr>
<td>Aa X Aa</td>
<td>4p^2q^2</td>
<td>p^2q^2</td>
</tr>
</tbody>
</table>

Expected disease frequency in these families:
\[ \frac{q^2}{(p+2q)^2} = \frac{q^2}{(1+q)^2} = 0.085^2/(1+0.085)^2 = 0.647\% \]

| 0.647% (expected) | Vs. | 0.61% (observed) |
Human Population Genetics

- Hardy-Weinberg Equilibrium
- Factors affect H-W Equilibrium
Factors that Alter Genetic Equilibrium

- Mutation
- Selection
- Genetic Drift
- Isolation
- Migration
- Consanguineous Marriage
Factors affect H-W Equilibrium

- Nonrandom mating

- In human population, mating is seldom random
  - Defined by racial, ethnic, religious, or other criteria
  - Consanguinity- mating among close relatives, a special form of nonrandom mating in human population
  - Consanguinity does increase the proportion of homozygotes in the next generation, thereby exposing disadvantageous recessive phenotypes to selection. Such selection may in turn alter allele frequencies in subsequent generations.
Nonrandom mating

- **Coefficient of relationship \((r)\)**: the proportion of all genes in two individuals which are identical by descent.

- **Inbreeding Coefficient \((F)\)**: The probability of identical homozygosity due to common ancestor
Factors affect H-W Equilibrium
- Nonrandom mating
Mutations in *BCKD-kinase* Lead to a Potentially Treatable Form of Autism with Epilepsy

Branched Chain Ketoacid Dehydrogenase Kinase (BCKDK)

*Science 338, 394 (2012)*
Factors affect H-W Equilibrium - Mutation

Generation

I  A  A  A  a  a  p=0.6; q=0.4

II A  A  a  a  a  p=0.4; q=0.6
Figure 2-3 Human Molecular Genetics, 3/e. (© Garland Science 2004)
2 breaks in same arm

Paracentric inversion

Interstitial deletion

2 breaks in different arms

Pericentric inversion

Ring chromosome

Figure 2-20  Human Molecular Genetics, 3/e.  (© Garland Science 2004)
Exchange of centric and acentric fragments leads to a reciprocal translocation. This results in dicentric and acentric chromosomes, which are not stable in mitosis.

Exchange of two acentric fragments also leads to a reciprocal translocation, resulting in stable reciprocal translocation.

Robertsonian translocation occurs through an exchange in proximal short arms, resulting in stable Robertsonian translocation with satellites and a lost segment.

Figure 2-21 Human Molecular Genetics, 3/e. (© Garland Science 2004)
Association between Microdeletion and Microduplication at 16p11.2 and Autism

Figure 1. A Hot Spot of Genomic Instability Associated with Autism.
Interspersed duplication blocks (12 and 13) on 16p11.2 promote unequal crossing over during meiosis (two of four chromosomes are shown). Gametes are produced that either lack or carry a double dose of the critical interval. Dosage-sensitive differences of genes in the critical interval (A, B, C) probably increase the susceptibility to disease. There are more than 25 genes or transcripts in the critical interval (e.g., DOC2A, QPRT, and TBX6), as well as rapidly evolving genes in the flanking duplications.
Mutation

• Mutation is the ultimate source of genetic variation in the form of new alleles.
• Mutation can result in several different types of change in DNA sequences; these can either have no effect, alter the product of a gene, or prevent the gene from functioning.
• Studies in the fly *Drosophila melanogaster* suggest that if a mutation changes a protein produced by a gene, this will probably be harmful, with about 70 percent of these mutations having damaging effects, and the remainder being either neutral or weakly beneficial.
Mutation-2

• Mutations can involve large sections of DNA becoming duplicated, usually through genetic recombination

• These duplications are a major source of raw material for evolving new genes, with tens to hundreds of genes duplicated in animal genomes every million years. Most genes belong to larger families of genes of shared ancestry

• Novel genes are produced by several methods, commonly through the duplication and mutation of an ancestral gene, or by recombining parts of different genes to form new combinations with new functions.
Mutation-3

• Here, domains act as modules, each with a particular and independent function, that can be mixed together to produce genes encoding new proteins with novel properties.

• Another advantage of duplicating a gene (or even an entire genome) is that this increases redundancy; this allows one gene in the pair to acquire a new function while the other copy performs the original function.
Factors affect H-W Equilibrium - Selection

- Selection represents the action of environmental factors on a particular phenotype, and hence its genotype
  - Selection may be positive or negative
  - Selection is the consequence of differences of biological fitness \( f \). Therefore, selection coefficient \( s = 1 - f \)
  - Biological fitness \( f \) is a measure of fertility
Diet and the evolution of human amylase gene copy number variation

![Graphs showing AMY1 diploid copy number variation and AMY1 protein concentration](image-url)
Figure 1 The distribution of salivary amylase copy number in the seven samples from Perry et al.\textsuperscript{1} The bar chart depicts the mean copy number per sample, with an interval of two standard errors above the mean. Mean copy number is found to be higher in populations with high-starch diets, even when samples are relatively near one another geographically (for example, comparing Hadza and Datog or Yakut and Japanese populations).
Sickle cell disease: Heterozygosity advantage
Lactose intolerance
Lactose intolerance and lactase persistence

• The *LCT* gene provides the instructions for making lactase.

• The specific DNA sequence in the *MCM6* gene “minichromosome maintenance complex component 6.” helps control whether the *LCT* gene is turned on or off.

• Possibly years ago, some humans developed a mutation in the *MCM6* gene that keeps the *LCT* gene turned on even after breast feeding is stopped.

• Lactase activity persistence in adults is associated with two polymorphisms: C/T 13910 and G/A 22018 located in the *MCM6* gene.
Selection for/against dominant alleles is efficient

- Mutant allele encoding dominant traits are expressed in heterozygotes and thus exposed to direct selection

  - Aa

  - aa

- A very weak selective change can rapidly alter the allele frequency
Selection for/against recessive alleles is inefficient

- Why? - because then most recessive alleles are in heterozygotes
- Thus, rare disease-causing recessive alleles persist in the population in heterozygote carriers, even if they are lethal when homozygous
Selection for/against recessive alleles is inefficient

\[
\frac{\text{# alleles in carriers}}{\text{# alleles in affected}} = \frac{2pq}{2q^2} \approx \frac{1}{q}
\]

\[q^2 = 1/10,000; \; q = 1/100, \ldots\]
Carrier/Affected Ratio for an autosomal recessive disease

<table>
<thead>
<tr>
<th>Disease Incidence</th>
<th>Carrier Frequency</th>
<th>Ratio Carrier/Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.43</td>
<td>4.3</td>
</tr>
<tr>
<td>0.01</td>
<td>0.18</td>
<td>18.0</td>
</tr>
<tr>
<td>0.001</td>
<td>0.06</td>
<td>61.2</td>
</tr>
<tr>
<td>0.0001</td>
<td>0.02</td>
<td>198.0</td>
</tr>
</tbody>
</table>

$q^2$  $2pq$
Selection against /for X-linked recessive alleles

- Efficiency: AD>XR>AR
A popular idea early in the 20th century was “eugenics”, improving the human population through selective breeding. The idea has been widely discredited, largely due to the evils of “forced eugenics” practiced in certain countries before and during World War 2. We no longer force “genetically defective” people to be sterilized.

However, note that positive eugenics: encouraging people to breed with superior partners, is still practiced in places.

The problem with sterilizing “defectives” is that most genes that produce a notable genetic diseases are recessive: only expressed in heterozygotes. If you only sterilize the homozygotes, you are missing the vast majority of people who carry the allele.

For example, assume that the frequency of a gene for a recessive genetic disease is 0.001, a very typical figure. Thus $p = 0.999$ and $q = 0.001$. Thus $p^2 = 0.998$, $2pq = 0.002$, and $q^2 = 0.000001$. The ratio of heterozygotes (undetected carriers) to homozygotes (people with the disease) is 2000 to 1: you are sterilizing only 1/2000 of the people who carry the defective allele. This is simply not a workable strategy for improving the gene pool.
Nazi Eugenics

"The Threat of the Underman. It looks like this: Male criminals had an average of 4.9 children, criminal marriage, 4.4 children, parents of slow learners, 3.5 children, a German family 2.2 children, and a marriage from the educated circles, 1.9 children."
Rate of *de novo* mutations and the importance of father’s age to disease risk


- A 36-year-old will pass on twice as many mutations to his child as a man of 20, and a 70-year-old eight times as many, Stefánsson’s team estimates.

- The researchers estimate that an Icelandic child born in 2011 will harbour 70 new mutations, compared with 60 for a child born in 1980; the average age of fatherhood rose from 28 to 33 over that time.

This explains 97.1% (90% confidence interval: 84.3%, 100%) of the remaining variation and the rate of paternal mutations is estimated to increase by 4.28% per year, which corresponds to doubling every 16.5 years and increasing by 8-fold in 50 years. Seventy-six of the 78 trios have father’s ages between 18 and 40.5, a range in which the differ-
Paternal Age and Risk of Schizophrenia

- Estimated cumulative incidence and percentage of offspring estimated to have an onset of schizophrenia by age 34 years, for categories of paternal age. The numbers above the bars show the proportion of offspring who were estimated to have an onset of schizophrenia by 34 years of age.

- Source: Malaspina et al., Arch Gen Psychiatry. 2001.
Factors affect H-W Equilibrium

- Genetic drift

- Change in a populations allele frequency due to chance - characteristic of small populations
Before:
8 RR  →  0.50 R
8  rr  →  0.50 r

After:
2 RR  →  0.25 R
6  rr  →  0.75 r
Factors affect H-W Equilibrium - Genetic drift

<table>
<thead>
<tr>
<th>Generation</th>
<th>Genotype</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A A A a a a</td>
<td>p=0.6; q=0.4</td>
</tr>
<tr>
<td>II</td>
<td>A A a a a a</td>
<td>p=0.5; q=0.5</td>
</tr>
<tr>
<td>III</td>
<td>a a a a a a</td>
<td>p=0; q=1</td>
</tr>
<tr>
<td>IV</td>
<td>a a a a a a</td>
<td>q=1</td>
</tr>
<tr>
<td>N</td>
<td>a a a a a a</td>
<td>q=1</td>
</tr>
</tbody>
</table>
Random Genetic Drift

Frequency of allele A

Generation

Random Genetic Drift

Frequency of allele A
Random Genetic Drift

- ABO frequency of American indians
  - North America: $I^A 0.018; I^B 0.009; i 0.973$
  - Blackfeet: $I^A 0.5$
Factors affect H-W Equilibrium -migration (Gene flow and transfer)

Generation

I  A  A  A  a  a  
   p=0.6; q=0.4

II  A  A  A  a  a  
   p=0.5; q=0.5

   A  a  a  
   p=0.5; q=0.5
Factors affect H-W Equilibrium - Founder effect

- Founder effect
  - A few individuals colonize a new habitat
  - Probably accounts for high frequency of inherited disorders in some human population
Founder Effect Example

- Founder effect example: the Amish are a group descended from 30 Swiss founders who renounced technological progress. Most Amish mate within the group. One of the founders had Ellis-van Crevald syndrome, which causes short stature, extra fingers and toes, and heart defects. Today about 1 in 200 Amish are homozygous for this syndrome, which is very rare in the larger US population.

- Note the effect inbreeding has here: the problem comes from this recessive condition becoming homozygous due to the mating of closely related people.
Huntington’s disease
• Alternative explanations of the high frequency of type O blood in American Indians:

• The founder effect: Was the O allele exceptionally common among the first Americans.

• Natural Selection: Malaria resistance of A and B vs. losses of OA and OB fetuses
Time to Most Recent Common Ancestor (TMRCA)

• Archeological evidence
  – origin in Africa 50-100kya
  – spread to rest of world, 50-60kya
• What does genetic evidence say?
• What about the location?
Mitochondrial “Eve”

• Most recent *matrilineal* common ancestor of all living humans
• All our mitochondria are descended from hers
• Does *not* mean she was the only human female alive at the time
  – Consider the set S of all humans alive today
  – Take the set S’ = mothers-of(S). (now all female)
  – Size(S’) ≤ Size (S)
  – ...continue until you have one member: that’s Eve
• Members of S have other female ancestors, but Eve is the only one with an unbroken matrilineal line to all of S
• She lived ~230kya
• She was not Eve during her own lifetime
  – Title of Eve depends on current set of people alive
  – as matrilineal lines die out, you get a more recent Eve
• Difficult to determine if she was *Homo sapiens*
Y-chromosome “Adam”

• Part of the Y chromosome does not recombine
• Hence we can do a similar trick
  – However, only men (XY) carry the Y chromosome
  – So we can only identify the most recent patrilineal common ancestor of all men living today:
• Estimated to live ~100kya
  – never met “Eve”!

• Why are mtDNA and Y chromosome TMRCA dates so different?
  – lower \( N_E \) for males than for females?
    • polygyny more frequent than polyandry?
    • higher male mortality rates?
    • higher male variability in reproductive success?
  – patrilocal marriage more common than matrilocal?
  – mtDNA mutation rates variable, causing error?
Fig. 3 The migration of modern *Homo sapiens*. The scheme outlined above begins with a radiation from East Africa to the rest of Africa about 100 kya and is followed by an expansion from the same area to Asia, probably by two routes, southern and northern between 60 and 40 kya. Oceania, Europe and America were settled from Asia in that order.

Current consensus: ~1,000 individuals (a tribe) left Africa 100kya...
Bottlenecks

• A population bottleneck is essentially the same phenomenon as the founder effect, except that in a bottleneck, the entire species is wiped out except for a small group of survivors. The allele frequencies in the survivors determines the allele frequencies in the population after it grows large once again.

• Example: Pingalop atoll is an island in the South Pacific. A typhoon in 1780 killed all but 30 people. One of survivors was a man who was heterozygous for the recessive genetic disease achromatopsia. This condition caused complete color blindness. Today the island has about 2000 people on it, nearly all descended from these 30 survivors. About 10% of the population is homozygous for achromatopsia. This implies an allele frequency of about 0.26.
The Island of the Colorblind

- The population of Pingelap island in Micronesia has an unusually high (5%) frequency of achromatopsia, a hereditary form of color blindness.

- Complete achromatopsia is a rare, autosomal recessive disorder characterized by a total inability to distinguish colours.

- A typhoon that reduced the island’s population to a small number of people and subsequent inbreeding appear to have increased the recessive allele responsible for the disease.
Human Bottleneck

• The human population is thought to have gone through a population bottleneck about 100,000 years ago. There is more genetic variation among chimpanzees living within 30 miles of each other in central Africa than there is in the entire human species.

• The tree represents mutational differences in mitochondrial DNA for various members of the Great Apes (including humans).
Which mammal has the most size variation?
Which mammal has the most size variation?
Human Genetic Variation
With the exception of monozygotic twins, which are NEARLY identical genetically, every one of us is genetically different from every other human who ever lived.
Geographic distribution of skin and hair color

Clinal distribution of hair color among Australian Aborigines

Discontinuous distribution of red hair in Britain

Distribution of Human Skin Color

Frequency of Yellow-brown Hair

- 0%
- 1-19.9%
- 20-39.9%
- 40-59.9%
- 60-79.9%
- 80-100%

Human Skin Color Distribution

- higher numbers represent darker skin color

- 1-12: 21-23
- 12-14: 24-26
- 15-17: 27-29
- 18-20: 30+

frequency of people with red hair

- 0-5%
- 5-10%
- 10-15%
- >15%
How are genomes of individuals different from one another?

More than 90% of the differences are single base substitutions. These are called single nucleotide polymorphisms (SNPs)
Any two human genomes are roughly 99.9% identical.


<table>
<thead>
<tr>
<th>Region</th>
<th>chr.</th>
<th>n</th>
<th>bp</th>
<th>S</th>
<th>π (%)</th>
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<tbody>
<tr>
<td>LPL</td>
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<tr>
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<td>X</td>
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<td>1147</td>
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<td>0</td>
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<tr>
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<td>X</td>
<td>10</td>
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<td>0</td>
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<td>–</td>
<td>14</td>
<td>2000000</td>
<td>2748</td>
<td>0.046</td>
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<tr>
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<td>–</td>
<td>114</td>
<td>196200</td>
<td>560</td>
<td>0.051</td>
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<tr>
<td>VDA survey</td>
<td>–</td>
<td>148</td>
<td>190000</td>
<td>874</td>
<td>–</td>
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</tbody>
</table>

chr - chromosome  
n - Number of samples examined  
S - Number of polymorphic sites  
π - Nucleotide divergence  

Mean = ~ 0.1%
The DNA Between Individuals is Identical.
All differences are in the 0.1% of DNA that varies.

It’s hard to believe sometimes!
There are non major genetic differences across ‘races’
= NO ‘races’

“The possibility that human history has been characterized by genetically relatively homogeneous groups (‘races’), distinguished by major biological differences, is not consistent with genetic evidence.”

What is Public Health Genetics?

- Public Health Genetics is defined as the application of advances in genetics and molecular biotechnology to improve public health and prevent disease.

University of Washington
Your Genetic ID Card?!

- The day of the personal DNA profile provided at birth, complete with calculated risks of various cancers, heart disease, and many other conditions could be actuality by the time that current first-year medical students begin to practice medicine.

- E. Hoffman Am J Hum Genet 1994
Genetics:
“The Next Revolution in Public Health”

• Medicine
  • Public Health

• Drugs for treatment and prophylaxis that are individually tailored to each person’s genetic background

  Prevention strategies involving behavioral, environmental, social and nutritional factors that are individually tailored to each person’s genetic background
Assurance and Evaluation Examples

- CDC Newborn Screening Quality Assurance Program
- Evaluation of Morbidity/Mortality from Sickle Cell Disease Following Newborn Screening
Genetic variation may be important from a medical point of view

For example, because of genetic differences, different people may respond differently to the same drug

- In the 1950s, anesthesiologists began using the muscle relaxant succinylcholine
- Succinylcholine is normally metabolized by cholinesterase
- One out of 2,500 people are heterozygous for a variant of cholinesterase that does not metabolize succinylcholine
- These people are OK unless exposed to succinylcholine, in which case they go into breathing arrest
Drugs By Design

• Talk to anyone in the pharmaceutical industry, you will discover that genetics is the biggest thing to hit drug research since a penicillium mold floated into Alexander Flemings’ petri dish.

• *Time*, January 11, 1999
Pharmacogenomics

“The Next Revolution In Medicine”

- In the very near future, primary care physicians will routinely perform genetic tests before writing a prescription because (they will) want to identify the poor responders.

- Francis Collins M.D, Director, NHGRI

- American Academy of Family Physicians Annual Meeting 1998
Figure 2. Typical Pattern of Stevens–Johnson Syndrome. Blisters develop on widespread purpuric macules.
Medical genetics

A marker for Stevens–Johnson syndrome

Wen-Hung Chung*, Shuen-Iu Hung†,
Hong-Shang Hong*, Mo-Song Hsia‡,
Li-Cheng Yang*, Hsin-Chun Ho*,
Jer-Yuarn Wu†§, Yuan-Tsong Chen†¶

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University Hospital, Taichung, Taiwan
¶Department of Pediatrics, Duke University Medical
Center, Durham, North Carolina 27710, USA
### Table 1  Frequency of HLA alleles in patients with Stevens–Johnson syndrome

<table>
<thead>
<tr>
<th>HLA allele</th>
<th>CBZ–SJS</th>
<th>CBZ-tolerant</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>B*1502</td>
<td>44 (100%)</td>
<td>3 (3%)*</td>
<td>8 (8.6%)†</td>
</tr>
<tr>
<td>Cw*0801</td>
<td>41 (93.2%)</td>
<td>17 (16.8%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>A*1101</td>
<td>36 (81.8%)</td>
<td>51 (50.5%)</td>
<td>53 (57%)</td>
</tr>
<tr>
<td>DRB1*1202</td>
<td>33 (75%)</td>
<td>12 (11.9%)</td>
<td>18 (19.4%)</td>
</tr>
<tr>
<td>B<em>1502, Cw</em>0801</td>
<td>41 (93.2%)</td>
<td>3 (3%)</td>
<td>7 (7.5%)</td>
</tr>
<tr>
<td>B<em>1502, A</em>1101</td>
<td>36 (81.8%)</td>
<td>2 (2%)</td>
<td>6 (6.5%)</td>
</tr>
<tr>
<td>B<em>1502, DRB1</em>1202</td>
<td>33 (75%)</td>
<td>1 (1%)</td>
<td>5 (5.4%)</td>
</tr>
<tr>
<td>B<em>1502, Cw</em>0801, A<em>1101, DRB1</em>1202</td>
<td>29 (66%)</td>
<td>0 (0%)</td>
<td>3 (3.2%)</td>
</tr>
</tbody>
</table>

Frequencies (by number and percentage) of individual or combined loci of the B*1502 ancestral haplotype are shown in patients with carbamazepine-induced Stevens–Johnson syndrome (CBZ–SJS; n = 44), and in carbamazepine-tolerant (n = 101) and normal subjects (n = 93). For methods, see supplementary information.

*Odds ratio (CBZ–SJS/CBZ-tolerant): 2,504 (95% CI, 126–49,522); corrected P value \( P_\text{c} = 3.13 \times 10^{-27} \).

†Odds ratio (CBZ–SJS/normal): 895 (95% CI, 50–15,869); \( P_\text{c} = 1.38 \times 10^{-21} \).