Physical Basis of Evolution

- DNA can replicate
- DNA can mutate and recombine
- DNA encodes information that interacts with the environment to influence phenotype

Phenotype is any measurable trait.

Mendelian Genotypes Are Always Discrete, But Phenotypes Can Be Either Discrete or Continuous.

This Presented A Serious Problem for Mendelism
### Genetic Disease in Humans

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence (Percent of Live Births)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendelian</td>
<td>1.25%</td>
</tr>
<tr>
<td>Chromosomal</td>
<td>1.65%</td>
</tr>
<tr>
<td>Irregularly Inherited</td>
<td>9.00%</td>
</tr>
<tr>
<td></td>
<td>(low penetrance, interactions with environments, oncogenes)</td>
</tr>
<tr>
<td>Polygenic Traits with $h^2 &gt; 0.3$</td>
<td>65.41%</td>
</tr>
<tr>
<td><strong>TOTAL:</strong></td>
<td>77.31%</td>
</tr>
</tbody>
</table>

Sickle-Cell Anemia is
A Single Locus, Autosomal
Recessive Genetic Disease

But is it?
First Complication:

Which Phenotype and Which Environment?

The Sickle Cell Mutation

![Diagram of normal and sickle cell hemoglobin molecules with DNA sequences]

<table>
<thead>
<tr>
<th>Normal hemoglobin</th>
<th>Hemoglobin S</th>
</tr>
</thead>
<tbody>
<tr>
<td>...ACT CT GAG GAG ...</td>
<td>...ACT CCT GTG GAG ...</td>
</tr>
</tbody>
</table>

- Valine
- Histidine
- Leucine
- Threonine
- Proline
- Glutamic acid
The Hemoglobin Molecule

Sickle-Cell is A Single Locus, Autosomal Codominant Allele for Electrophoretic Mobility

<table>
<thead>
<tr>
<th>Organismic phenotype</th>
<th>Genotype</th>
<th>Positions to which hemoglobin have migrated</th>
<th>Origin</th>
<th>Hemoglobin types present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle-cell trait</td>
<td>$H_b^S/H_bA$</td>
<td></td>
<td></td>
<td>S and A</td>
</tr>
<tr>
<td>Sickle-cell anemia</td>
<td>$H_b^S/H_bS$</td>
<td></td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Normal</td>
<td>$H_b^A/H_bA$</td>
<td></td>
<td></td>
<td>A</td>
</tr>
</tbody>
</table>

Migration
Allosteric Shifts in Hemoglobin

Beta-Hemoglobin S Molecules Can Bond With Adjacent Alpha-Hb Molecules After Losing O$_2$, Starting a Polymerization Reaction that forms long alpha-helices of Hb Molecules. Can distort cell shape (sickling) and even lyse the cell, leading to anemia.
Sickle-Cell is A Single Locus, Autosomal Dominant Allele for the Sickling Trait Under the Environmental Conditions of Low Oxygen Tension

The Low O$_2$ Conditions That Can Induce Sickling Include:

- Loss of Oxygen in Capillaries
- High Altitudes
- Pregnancy
- Infection of a Red Blood Cell By a Malarial Parasite
Infection of a Red Blood Cell By a Malarial Parasite

- Sickle-Cells Are Filtered Out Preferentially by the Spleen
- Malaria Infected Cells Are Often Filtered Out Because of Sickling Before the Parasite Can Complete Its Life Cycle
- The Sickle Cell Allele is Therefore an Autosomal, Dominant Allele for Malarial Resistance.

Loss of Oxygen in Capillaries

- Capillaries Only Allow 1 Red Blood Cell To Pass At a Time
- Sickling Is More Extreme in SS Homozygotes
- Extremely Deformed Sickle Cells Often Cannot Pass Through the Capillary, Causing Local Failures of Blood Supply
- Extremely Deformed Sickle Cells Often Burst
The Sickle Cell Anemia Phenotype

Sickle-Cell Allele is An Autosomal Recessive for the Phenotype of Hemolytic Anemia
Most Deaths Due to Sickle Cell Anemia and Due to Malaria Occur Before Adulthood. Viability Is The Phenotype of Living To Adulthood

- In a non-Malarial Environment, The S Allele is a **Recessive Allele** For Viability Because Only the Homozygotes Get Sickle Cell Anemia.
- In a Malarial Environment, The S Allele is an **Overdominant Allele** For Viability Because Only the Heterozygotes Are Resistant to Malaria And Do Not Get Sickle Cell Anemia.

### Phenotypes at Different Levels of Analysis

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Normal AA</th>
<th>Carrier AS</th>
<th>Diseased SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-globin polypeptide production</td>
<td>Normal</td>
<td>Normal</td>
<td>More sickled cells</td>
</tr>
<tr>
<td>Red blood cell shape at sea level</td>
<td>Normal</td>
<td>Normal</td>
<td>Sicker cell shape</td>
</tr>
<tr>
<td>Red blood cell concentration at sea level</td>
<td>Normal</td>
<td>Lower</td>
<td>Lower</td>
</tr>
<tr>
<td>Red blood cell shape at high altitudes</td>
<td>Normal</td>
<td>Sickled cells present</td>
<td>Severe sickling</td>
</tr>
<tr>
<td>Red blood cell concentration at high altitudes</td>
<td>Normal</td>
<td>Lower</td>
<td>Very low, anemia</td>
</tr>
<tr>
<td>Susceptibility to malaria</td>
<td>Normal susceptibility</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>Viability in a non-malarial region</td>
<td>High</td>
<td>High</td>
<td>Low Because Of Anemia</td>
</tr>
<tr>
<td>Viability in a malarial region</td>
<td>Low Because Of Malaria</td>
<td>High</td>
<td>Low Because Of Anemia</td>
</tr>
</tbody>
</table>

**Dominance, Recessive, etc. Are Not Properties of Alleles But Refer to Genotype to Phenotype Relationships in an Environmental Specific Fashion**
Second Complication:
Interactions With Other Genes?
Genetic Backgrounds of the S Allele

On This Chromosomal Background, The S Allele Is Associated with Y Alleles That Do Not Completely Turn Off In Adults, Thereby Ameliorating the Clinical Symptoms of SS Individuals.
Genetic Backgrounds of the S Allele: Other Loci

The Sickle-Cell Allele is Necessary But Not Sufficient for Sickle Cell Anemia Because of Epistasis With Several Other Loci

Sickle-Cell Anemia is Therefore a Polygenic, Complex Genetic Disease
The Confoundment of Frequency and Apparent Causation in Systems of Interacting Factors

Phenylketonuria

- Compromised PH activity
- Increased breakdown products: Phenylacetic acid, Phenylactic acid, Orthohydroxyphenylacetic acid
- Clinical symptoms: Intellectual impairment, Skin disorders
$p/p$ fetus develops in Low Phenylalanine \textit{in utero} Environment

$p^+/p$ Mother Creates Low Phenylalanine \textit{in utero} Environment

$p/p$ Baby Born With Normal Brain

Low Phenylalanine Diet

Normal Diet

Mentally Retarded

$p^+/p$ fetus develops in High Phenylalanine \textit{in utero} Environment

$p/p$ Mother on Normal Diet Creates High Phenylalanine \textit{in utero} Environment

$p^+/p$ Baby Born With Abnormal Brain

Low Phenylalanine Diet

Normal Diet

Mentally Retarded

Mentally Retarded

Mentally Retarded
Note, mental retardation is NOT inherited; rather, a response to dietary environment is inherited.

**Scurvy**

- Ascorbic Acid (Vitamin C) Is Essential For Collagen Synthesis
- Most Mammals Can Synthesize Ascorbic Acid, But All Humans Are Homozygous For A Non-Functional Allele
Scurvy and PKU

Homozygosity for a Non-functional Allele

Enzyme Deficiency

Dietary Environment

Phenotype (Either Diseased or Normal)

Scurvy Is Called a Dietary Disease
PKU Is Called a Genetic Disease

WHY THE DIFFERENCE?
The Confoundment of Frequency and Apparent Causation in Systems of Interacting Factors

Factors That Are Rare Are More Strongly Associated With Phenotypic Variation Than Factors That Are Common

The Disease Phenotype in PKU vs. Scurvy

<table>
<thead>
<tr>
<th></th>
<th>Genetic Factor</th>
<th>Dietary Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Scurvy</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>
The Confoundment of Frequency and Apparent Causation in Systems of Interacting Factors

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Disease</td>
<td>No Disease</td>
</tr>
<tr>
<td>A2</td>
<td>No Disease</td>
<td>No Disease</td>
</tr>
</tbody>
</table>

Let Frequency of A1 = 0.9, Frequency of A2 = 0.1
Frequency of B1 = 0.1, and Frequency of B2 = 0.9

Frequency in General Population = 0.09.
Frequency of the Disease Given A1 = Freq. (B1) = 0.1
Frequency of the Disease Given B1 = Freq. (A1) = 0.9

Causes of Variation of a Phenotype

Versus

Cause of a Phenotype
Ronald A. Fisher

- By Age 22 (1912) was laying the basis for much of modern statistics, but could not get an academic position
- In 1913 Became Convinced of Mendelism
- In 1916 submitted a paper that explained the inheritance of quantitative traits through Mendelian factors

Most Traits Are Influenced By Both Many Genes and Environmental Variation: Frequently Results in a Normal Distribution. E.g. Cholesterol in Framingham, MA

Relative Frequency in Population

Total Serum Cholesterol in mg/dl
By 1916, Fisher Realized

2. Therefore, what is important about an individual’s phenotype is not its value, but how much it deviates from the average of the population; That is, focus is on variation.
3. Quantitative inheritance could not be studied in individuals, but only among individuals in a population.
Fisher’s Model

\[ P_{ij} = \mu + g_i + e_j \]

The mean (average) phenotype for The entire population:
\[ \Sigma_i \Sigma_j P_{ij}/n \]
Where \( n \) is the number of individuals sampled.

Fisher’s Model

\[ P_{ij} = \mu + g_i + e_j \]

The genotypic deviation for genotype \( i \) is the Average phenotype of genotype \( i \) minus the Average phenotype of the entire population:
\[ g_i = \Sigma_j P_{ij}/n_i - \mu \]
Where \( n_i \) is the number of individuals with genotype \( i \).
Fisher’s Model

\[ P_{ij} = \mu + g_i + e_j \]

The environmental deviation is the deviation of an individual’s phenotype from the average phenotype of his/her genotype:

\[ e_j = P_{ij} - \frac{\sum_j P_{ij}}{n_i} = P_{ij} - (g_i + \mu) = P_{ij} - \mu - g_i \]

---

Although called the “environmental” deviation, \( e_j \) is really all the aspects of an individual’s phenotype that is not explained by genotype in this simple, additive genetic model.
Fisher’s Model

\[ \sigma^2_p = \text{Phenotypic Variance} \]
\[ \sigma^2_p = \text{Average}(P_{ij} - \mu)^2 \]
\[ \sigma^2_p = \text{Average}(g_i + e_j)^2 \]
Fisher’s Model

\[ \sigma^2_p = \text{Average}(g_i^2) + \text{Average}(2g_i e_j) + \text{Average}(e_j^2) \]

Because the “environmental” deviation is really all the aspects of an individual’s Phenotype that is not explained by genotype, This cross-product by definition has an average Value of 0.

Phenotypic Variance
Fisher’s Model

\[ \sigma_p^2 = \text{Average}(g_i^2) + \text{Average}(e_j^2) \]
\[ \sigma_p^2 = \sigma_g^2 + \sigma_e^2 \]

Genetic Variance

Fisher’s Model

\[ \sigma_p^2 = \text{Average}(g_i^2) + \text{Average}(e_j^2) \]
\[ \sigma_p^2 = \sigma_g^2 + \sigma_e^2 \]

Environmental Variance
(Really, the variance not Explained by the Genetic model)
Fisher’s Model

\[ \sigma^2_p = \sigma^2_g + \sigma^2_e \]

Phenotypic Variance = Genetic Variance + Unexplained Variance

In this manner, Fisher partitioned the causes of phenotypic variation into a portion explained by genetic factors and an unexplained portion.

Fisher’s Model

\[ \sigma^2_p = \sigma^2_g + \sigma^2_e \]

Phenotypic Variance = Genetic Variance + Unexplained Variance

This partitioning of causes of variation can only be performed at the level of a population.

An individual’s phenotype is an inseparable interaction of genotype and environment.
ApoE and Cholesterol in a Canadian Population

\[ \mu = 174.6 \]
\[ \sigma^2_p = 732.5 \]

\[
\begin{array}{c|c|c|c|c|c|c}
\hline
\text{H-W Freq.} & 0.592 & 0.121 & 0.234 & 0.006 & 0.024 & 0.023 \\
\hline
\text{Mean Pheno.} & 173.8 & 161.4 & 183.5 & 136.0 & 178.1 & 180.3
\end{array}
\]
### Step 1: Calculate the Mean Phenotype of the Population

<table>
<thead>
<tr>
<th>Genotype</th>
<th>3/3</th>
<th>3/2</th>
<th>3/4</th>
<th>2/2</th>
<th>2/4</th>
<th>4/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-W Freq.</td>
<td>0.592</td>
<td>0.121</td>
<td>0.234</td>
<td>0.006</td>
<td>0.024</td>
<td>0.023</td>
</tr>
<tr>
<td>Mean Phen.</td>
<td>173.8</td>
<td>161.4</td>
<td>183.5</td>
<td>136.0</td>
<td>178.1</td>
<td>180.3</td>
</tr>
</tbody>
</table>

\[ \bar{\mu} = (0.592)(173.8)+(0.121)(161.4)+(0.234)(183.5)+(0.006)(136.0)+(0.024)(178.1)+(0.023)(180.3) \]

\[ \bar{\mu} = 174.6 \]

### Step 2: Calculate the genotypic deviations

<table>
<thead>
<tr>
<th>Genotype</th>
<th>3/3</th>
<th>3/2</th>
<th>3/4</th>
<th>2/2</th>
<th>2/4</th>
<th>4/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Phen.</td>
<td>173.8</td>
<td>161.4</td>
<td>183.5</td>
<td>136.0</td>
<td>178.1</td>
<td>180.3</td>
</tr>
<tr>
<td>( g_i )</td>
<td>173.8-174.6</td>
<td>161.4-174.6</td>
<td>183.5-174.6</td>
<td>136.0-174.6</td>
<td>178.1-174.6</td>
<td>180.3-174.6</td>
</tr>
<tr>
<td>( g_i )</td>
<td>-0.8</td>
<td>-13.2</td>
<td>8.9</td>
<td>-38.6</td>
<td>3.5</td>
<td>5.7</td>
</tr>
</tbody>
</table>

\[ \mu = 174.6 \]
Step 3: Calculate the Genetic Variance

<table>
<thead>
<tr>
<th>Genotype</th>
<th>3/3</th>
<th>3/2</th>
<th>3/4</th>
<th>2/2</th>
<th>2/4</th>
<th>4/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-W Freq.</td>
<td>0.592</td>
<td>0.121</td>
<td>0.234</td>
<td>0.006</td>
<td>0.024</td>
<td>0.023</td>
</tr>
<tr>
<td>gi</td>
<td>-0.8</td>
<td>-13.2</td>
<td>8.9</td>
<td>-38.6</td>
<td>3.5</td>
<td>5.7</td>
</tr>
</tbody>
</table>

\[ \sigma_g^2 = (0.592)(-0.8)^2 + (0.121)(-13.2)^2 + (0.234)(8.9)^2 + (0.006)(-38.6)^2 + (0.024)(3.5)^2 + (0.023)(5.7)^2 \]

\[ \sigma_g^2 = 50.1 \]

Step 4: Partition the Phenotypic Variance into Genetic and “Environmental” Variance

\[ \sigma_p^2 = 732.5 \]

\[ \sigma_g^2 = 50.1 \]

\[ \sigma_e^2 = 682.4 \]
Broad-Sense Heritability

\( h^2_B \) is the proportion of the phenotypic variation that can be explained by the modeled genetic variation among individuals.

For example, in the Canadian Population for Cholesterol Level

\[ h^2_B = \frac{50.1}{732.5} = 0.07 \]

That is, 7% of the variation in cholesterol levels in this population is explained by genetic variation at the ApoE locus.
Broad-Sense Heritability

Genetic Variation at the ApoE locus is therefore a cause of variation in cholesterol levels in this population.

ApoE does not “cause” an individual’s cholesterol level.

An individual’s phenotype cannot be partitioned into genetic and unexplained factors.

Broad-Sense Heritability

Measures the importance of genetic Variation as a Contributor to Phenotypic Variation Within a Generation

The more important (and difficult) question is how Phenotypic Variation is Passed on to The Next Generation.
**Fisher’s Model**

1. Assume that the distribution of environmental deviations ($e_j$’s) is the same every generation
2. Assign a “phenotype” to a gamete
Phenotypes of Gametes

1. Average Excess of a Gamete Type
2. Average Effect of a Gamete Type

3. These two measures are identical in a random mating population, so we will consider only the average excess for now.

The Average Excess

The Average Excess of Allele $i$ is the average genotypic deviation caused by a gamete bearing allele $i$ after fertilization with a second gamete drawn from the gene pool according to the deme’s system of mating.
The Average Excess

\[ a_i = \frac{t_{ii}}{p_i} g_{ii} + \sum_{j \neq i} \frac{1}{2} t_{ij} g_{ij} = \sum_j t(ij \mid i) g_{ij} \]

Where \( g_{ij} \) is the genotypic deviation of genotype \( ij \), \( t_{ij} \) is the frequency of \( ij \) in the population (not necessarily HW), \( p_i \) is the frequency of allele \( i \), and:

\[
\begin{align*}
\text{Prob}(ii \text{ given } i) &= t(ii \mid i) = \frac{t_{ii}}{p_i} \\
\text{Prob}(ij \text{ given } i) &= t(ij \mid i) = \frac{1}{2} t_{ij} \frac{p_i}{p_i} = \frac{1}{2} t_{ij} p_i \\
\text{when } j \neq i
\end{align*}
\]

The Average Excess

Note, under random mating \( t_{ii} = p_i^2 \) and \( t_{ij} = 2p_ip_j \), so:

\[
\begin{align*}
\text{Prob}(ii \text{ given } i) &= t(ii \mid i) = \frac{t_{ii}}{p_i} = p_i \\
\text{Prob}(ij \text{ given } i) &= t(ij \mid i) = \frac{1}{2} t_{ij} = p_j \\
\text{when } j \neq i
\end{align*}
\]

\[ a_i = \sum_j p_j g_{ij} \]
Random Mating

<table>
<thead>
<tr>
<th>Deme</th>
<th>3/3</th>
<th>3/2</th>
<th>3/4</th>
<th>2/2</th>
<th>2/4</th>
<th>4/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.592</td>
<td>0.121</td>
<td>0.234</td>
<td>0.006</td>
<td>0.024</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Average Excess of An Allele

<table>
<thead>
<tr>
<th>Gene Pool</th>
<th>ε2</th>
<th>ε3</th>
<th>ε4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.078</td>
<td>0.770</td>
<td>0.152</td>
</tr>
</tbody>
</table>

What Genotypes Will an ε2 allele find itself in after random mating?
Random Mating
Gene Pool
Deme

What are the probabilities of these Genotypes after random mating given an $\epsilon_2$ allele?

These are the Conditional Probabilities of the genotypes Given random mating and a gamete with the $\epsilon_2$ allele.
Average Excess of An Allele

Gene Pool

<table>
<thead>
<tr>
<th>Allele</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε2</td>
<td>0.078</td>
</tr>
<tr>
<td>ε3</td>
<td>0.770</td>
</tr>
<tr>
<td>ε4</td>
<td>0.152</td>
</tr>
</tbody>
</table>

Random Mating

<table>
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<tr>
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<th>Allele</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/3</td>
<td>3/2</td>
<td>2/2 2/4</td>
</tr>
<tr>
<td>0.770</td>
<td>0.078</td>
<td>0.152</td>
</tr>
</tbody>
</table>

Development

Genotypic Deviations

<table>
<thead>
<tr>
<th>Environment</th>
<th>Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>-13.2</td>
<td>-38.6</td>
</tr>
<tr>
<td>3.5</td>
<td></td>
</tr>
</tbody>
</table>

Average Genotypic Deviation of a ε2 bearing gamete =

\[(0.770)(-13.2)+(0.078)(-38.6)+(0.152)(3.5) = -12.6\]

Average Excess of Allele ε3

Gene Pool

<table>
<thead>
<tr>
<th>Allele</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε2</td>
<td>0.078</td>
</tr>
<tr>
<td>ε3</td>
<td>0.770</td>
</tr>
<tr>
<td>ε4</td>
<td>0.152</td>
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</tbody>
</table>

Random Mating

<table>
<thead>
<tr>
<th>Deme</th>
<th>Allele</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
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<td>3/2</td>
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<td>0.770</td>
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</tr>
</tbody>
</table>

Development

Genotypic Deviations

<table>
<thead>
<tr>
<th>Environment</th>
<th>Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.8</td>
<td>-13.2</td>
</tr>
<tr>
<td>8.9</td>
<td></td>
</tr>
</tbody>
</table>

Average Excess of ε3 =

\[(0.770)(-0.8)+(0.078)(-13.2)+(0.152)(8.9) = -0.3\]
Average Excess of Allele $\varepsilon 4$

Gene Pool

Random Mating

Deme

Development

Genotypic Deviations

Environment

Average Excess of $\varepsilon 4 = (0.770)(8.9)+(0.078)(3.5)+(0.152)(5.7) = 8.0$

Gene Pool

Alleles

Frequencies

"Phenotype"

(Average Excess)

The critical breakthrough in Fisher’s paper was assigning a “phenotype” to a gamete, the physical basis of the transmission of phenotypes from one generation to the next.
Average Excess of $\epsilon 4 = (0.770)(8.9) + (0.078)(3.5) + (0.152)(5.7) = 8.0$

The Average Excess Depends Upon the Genotypic Deviations, which in turn Depend Upon the Average Phenotypes of the Genotypes and And the Average Phenotype of the Deme, which in turn Depends Upon The Genotype Frequencies.

Average Excess of $\epsilon 4 = (0.770)(8.9) + (0.078)(3.5) + (0.152)(5.7) = 8.0$

The Average Excess Depends Upon the Gamete Frequencies in the Gene Pool and Upon the System of Mating.
The Average Excess

The Portion of Phenotypic Variation That Is Transmissible Through a Gamete Via Conditional Expectations

The Average Effect

The Portion of Phenotypic Variation That Is Transmissible Through a Gamete Measured At the Level of a Deme and Its Associated Gene Pool via Least-Squares Regression.
The Average Effect

Templeton (1987) showed:

\[ \alpha_i = \frac{a_i}{1 + f} \]

Fisher’s Model

The Next Step Is To Assign a “Phenotypic” Value To a Diploid Individual That Measures Those Aspects of Phenotypic Variation That Can be Transmitted Through the Individual’s Gametes.

Breeding Value or Additive Genotypic Deviation Is The Sum of the Average Effects (=Average Excesses Under Random Mating) of Both Gametes Borne By An Individual.
Additive Genotypic Deviation

Let $k$ and $l$ be two alleles (possibly the same) at a locus of interest. Let $\alpha_k$ be the Average Effect of allele $k$, and $\alpha_l$ the Average Effect of allele $l$. Let $g_{kl}$ be the additive genotypic deviation of genotype $k/l$. Then:

$$g_{kl} = \alpha_k + \alpha_l$$

<table>
<thead>
<tr>
<th>Genotype</th>
<th>3/3</th>
<th>3/2</th>
<th>3/4</th>
<th>2/2</th>
<th>2/4</th>
<th>4/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-W Freq.</td>
<td>0.592</td>
<td>0.121</td>
<td>0.234</td>
<td>0.006</td>
<td>0.024</td>
<td>0.023</td>
</tr>
<tr>
<td>$g_i$</td>
<td>-0.8</td>
<td>-13.2</td>
<td>8.9</td>
<td>-38.6</td>
<td>3.5</td>
<td>5.7</td>
</tr>
</tbody>
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<tr>
<th>Alleles</th>
<th>$\varepsilon_2$</th>
<th>$\varepsilon_3$</th>
<th>$\varepsilon_4$</th>
</tr>
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<tbody>
<tr>
<td>Frequencies</td>
<td>0.078</td>
<td>0.770</td>
<td>0.152</td>
</tr>
<tr>
<td>Average Excess</td>
<td>-12.6</td>
<td>-0.3</td>
<td>8.0</td>
</tr>
<tr>
<td>$g_{ai}$</td>
<td>-0.3+(-0.3)</td>
<td>-0.3+(-12.6)</td>
<td>-0.3+8.0</td>
</tr>
<tr>
<td></td>
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### The Additive Genetic Variance

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<td>-4.6</td>
<td>16.0</td>
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</tbody>
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$\sigma^2_a = \sum (g_i)^2 = (0.592)(-0.6)^2 + (0.121)(-12.9)^2 + (0.234)(7.7)^2 + (0.006)(-25.4)^2 + (0.024)(-4.6)^2 + (0.023)(16.0)^2$

$\sigma^2_a = 44.7$

### The Additive Genetic Variance

Note that $\sigma^2_g = 50.1 > \sigma^2_a = 44.7$

It is always true that $\sigma^2_g > \sigma^2_a$

Have now subdivided the genetic variance into a component that is transmissible to the next generation and a component that is not:

$\sigma^2_g = \sigma^2_a + \sigma^2_d$
The Additive Genetic Variance

\[ \sigma^2_g = \sigma^2_a + \sigma^2_d \]

The non-additive variance, \( \sigma^2_d \), is called the “Dominance Variance” in 1-locus models.

Mendelian dominance is necessary but not sufficient for \( \sigma^2_d > 0 \).

\( \sigma^2_d \) depends upon dominance, genotype frequencies, allele frequencies and system of mating.

The Additive Genetic Variance

For the Canadian Population,

\[ \sigma^2_g = 50.1 \text{ and } \sigma^2_a = 44.7 \]

Since \( \sigma^2_g = \sigma^2_a + \sigma^2_d \)

\[ 50.1 = 44.7 + \sigma^2_d \]

\[ \sigma^2_d = 50.1 - 44.7 = 5.4 \]
Partition the Phenotypic Variance into Additive Genetic, non-Additive Genetic and “Environmental” Variance

\[ \sigma_p^2 = \sigma_g^2 + \sigma_e^2 \]

\[ \sigma_g^2 = 732.5 \]

\[ \sigma_a^2 = 44.7 \]

\[ \sigma_d^2 = 5.4 \]

\[ \sigma_e^2 = 682.4 \]

The Additive Genetic Variance

\[ \sigma_g^2 = \sigma_a^2 + \sigma_d^2 + \sigma_i^2 \]

In multi-locus models, the non-additive variance is divided into the Dominance Variance and the Interaction (Epistatic) Variance, \( \sigma_i^2 \).

Mendelian epistasis is necessary but not sufficient for \( \sigma_i^2 > 0 \).

\( \sigma_i^2 \) depends upon epistasis, genotype frequencies, allele frequencies and system of mating.
The Partitioning of Variance

\[ \sigma_p^2 = \sigma_a^2 + \sigma_d^2 + \sigma_i^2 + \sigma_e^2 \]

As more loci are added to the model, \( \sigma_e^2 \) goes down relative to \( \sigma_g^2 \) such that \( h_B^2 = 0.65 \) for the phenotype of total serum cholesterol in this population. Hence, \textit{ApoE} explains about 10% of the heritability of cholesterol levels, making it the largest single locus contributor.

(Narrow-Sense) Heritability

\( h^2 \) is the proportion of the phenotypic variance that can be explained by the additive genetic variance among individuals.
(Narrow-Sense) Heritability

For example, in the Canadian Population for Cholesterol Level

\[ h^2 = \frac{44.7}{732.5} = 0.06 \]

That is, 6% of the variation in cholesterol levels in this population is transmissible through gametes to the next generation from genetic variation at the ApoE locus.