Multifactorial Inheritance: the Interplay of Genes and Environment
Virginia Pallante, M.S.

REQUIRED READING


Complete problems 1 - 3 from Chapter 8.

OBJECTIVES

1. Describe the differences between qualitative and quantitative traits.
2. Describe a model for the inheritance of quantitative traits.
3. Explain the threshold model of multifactorial inheritance, including the concept of liability.
4. Cite relevant factors in the assessment of risk to relatives, given the occurrence of a multifactorial threshold disease in a family.
5. Present the contribution of genetic factors to the correlation between relatives for a quantitative trait.

IMPORTANT TERMS

Multifactorial trait Qualitative trait
Threshold model Additive genetic effects
Quantitative trait Polygenic heritability
Recurrence risk Liability (level of risk)

1. Differences Between Single Gene and Multifactorial Inheritance

   A. Single gene disorders

      1. The presence or absence of a disorder is influenced by a mutation at a single genetic locus.

      2. Inheritance is typically Mendelian, however, it may be non-Mendelian as with genomic imprinting or mitochondrial
B. Multifactorial traits

1. Traits are influenced by a number of genes and non-genetic factors (i.e. environmental factors).
   a. When only genetic factors influence a trait, it is said to be **polygenic**.
   b. Multifactorial traits may be **quantitative** or **qualitative**.
      i. A **quantitative** trait can be measured on some continuous scale (e.g., blood pressure, height, weight, serum cholesterol). Quantitative traits often exhibit normal variation (where the differences among individuals are not pathologic), but the extremes of quantitative traits may be clinically relevant (e.g., high cholesterol levels). Quantitative traits which typically show normal variation among individuals may be altered by the influence of a gene of major effect (e.g., achondroplasia will influence normal variation in height).
      ii. A **qualitative** trait is an all or none phenotype. The presence or absence of a disease is a qualitative phenotype. Examples include diabetes, schizophrenia, non-syndromic open neural tube defects, and non-syndromic cleft lip and palate. In some cases, a quantitative trait underlies a qualitative trait (e.g., blood pressure and hypertension).

2. Multifactorial traits can be familial, but the pattern of inheritance is non-Mendelian.

3. Many common diseases have multifactorial inheritance: asthma, coronary artery disease, hypertension, obesity, autoimmune disorders, diabetes, depression, schizophrenia, substance abuse, epilepsy, most isolated birth defects (e.g. structural heart disease, cleft lip & palate, neural tube defects), and many cancers.

II. The Inheritance of Quantitative Multifactorial Traits
A. Inheritance is explained by a model which assumes that multifactorial traits are caused by the **additive** effects of many genes and environmental factors.

1. For a quantitative trait influenced by one gene with two alleles, there are three genotypes: AA, Aa, and aa. If allele A adds one unit to the trait and allele a adds nothing, then there are three possible values or phenotypes for the trait in a 1:2:1 ratio.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Trait Value</th>
<th># of Occurrence &amp; Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>2</td>
<td>1 (0.25)</td>
</tr>
<tr>
<td>Aa, aA</td>
<td>1</td>
<td>2 (0.50)</td>
</tr>
<tr>
<td>aa</td>
<td>0</td>
<td>1 (0.25)</td>
</tr>
</tbody>
</table>

Table 1

2. Now consider a quantitative trait influenced by two loci each with two alleles. Genotypes at the A locus (A or a) and B locus (B or b) have the following genotypic values. The A or B allele add one unit to the trait, while the a and b alleles add nothing. There are now five possible values for the trait (0 through 4; see the table below) in a 1:4:6:4:1 ratio.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Trait Value</th>
<th># of Occurrence &amp; Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>aabb</td>
<td>0</td>
<td>1 (0.0625)</td>
</tr>
<tr>
<td>Aabb, aAbb, aaBb, aabB</td>
<td>1</td>
<td>4 (0.25)</td>
</tr>
<tr>
<td>AAbb, AaBb, AabB, aABb, aABb, aABb, aAbB</td>
<td>2</td>
<td>6 (0.375)</td>
</tr>
<tr>
<td>AAbB, AaBB, AaBb, aABB</td>
<td>3</td>
<td>4 (0.25)</td>
</tr>
<tr>
<td>AABB</td>
<td>4</td>
<td>1 (0.0625)</td>
</tr>
</tbody>
</table>

Table 2

3. As additional loci and environmental factors are added, the distribution of the trait values smoothes out to approximate a normal distribution (a bell curve).
Part A: The distribution of height in a population, assuming that height is controlled by a single locus with genotypes AA, Aa, and aa.

Part B: The distribution of height, assuming that height is controlled by two loci. There are now five distinct phenotypes instead of three, and the distribution begins to look more like the normal distribution.

Part C: The distribution of height, assuming that multiple factors, each with a small effect, contribute to the trait (the multifactorial model).

III. The Inheritance of Qualitative Multifactorial Traits

A. The multifactorial threshold model has been adopted to explain the inheritance of qualitative traits which do not follow Mendelian patterns of inheritance.

   1. The sum of all genetic and environmental factors which contribute to a disorder constitute an individual’s liability (level of risk) to the disorder.
      
      a. Liability is assumed to be normally distributed. (The additive effects of genes and environmental influences, as described above, result in an individual’s liability).
      b. In most cases we do not have a measure of liability. There are exceptions such as blood pressure and hypertension.

   2. An individual expresses the disorder once his or her liability exceeds a given threshold.

   3. The higher the threshold, the more rare the disorder.

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B. Clinical characteristics of multifactorial traits.
1. The trait shows familial clustering but there is no distinctive Mendelian pattern of inheritance.

2. There are often sex differences in the frequency of the trait. This implies that the threshold may be different for males and females.

   a. Neural tube defects, systemic lupus erythematosus (SLE), and rheumatoid arthritis are more common in females.

   b. Pyloric stenosis, cleft lip and palate, and alcoholism are more common in males.

Figure 3
3. The **recurrence risk** of the disorder (the frequency of the disorder in the relatives of an affected individual) depends upon several factors.

   a. In many cases, the recurrence risk is proportional to the population risk of the trait, i.e. the more common the trait, the higher the risk of recurrence. Specifically, the recurrence risk in a first-degree relative is approximately equal to the square root of the incidence of the disorder in the population. Thus, the recurrence risk for a disorder with an incidence of 1/1000 is about 3%, while the recurrence risk for a disorder with frequency of 1/100 is about 10%. Note that for single gene disorders, the recurrence risk does not depend upon the population frequency of the condition. Rather it depends on the mode of inheritance and the degree of relatedness.

   b. The recurrence risk is the same for each type of relative that shares the same proportion of genes with the affected individual. For example, the recurrence risk for parents, siblings, and offspring of a proband are typically the same, because they are all first degree relatives of the proband and have 50% of their genes in common.

   c. The recurrence risk drops off very quickly as the relationship to the affected individual becomes more distant. For example the recurrence risk for non-syndromic cleft lip and palate is 4% for the sibling (first degree relative) of a proband but only 0.3% for the proband’s first cousin (third degree relative).

   d. The recurrence risk for a multifactorial disorder increases as the proband’s liability increases (i.e., as it becomes even greater than the threshold). An individual’s liability is increased if
      
      i. The proband has additional family members with the disorder.
      ii. The proband is more severely affected with the disorder.
      iii. The proband is of the less commonly affected sex.

**Application of Assessment of Recurrence Risk:**

In Couple A the husband has a non-syndromic unilateral cleft lip and palate and in Couple B the wife has a non-syndromic unilateral cleft lip and palate. Which couple is at higher risk to have a child with cleft lip and palate? Are sons and daughters at the same risk and if not, who is at higher risk?

*Answer is at the end of the syllabus*
C. Counseling a family

1. For multifactorial traits, risk estimates are empirical - estimated from the experience of many families.

2. CL/P is more common in males and has a higher incidence in Native American Indians and Asians.

<table>
<thead>
<tr>
<th>Clinical Correlation: Cleft lip and cleft palate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of disorder: 1/1,000</td>
</tr>
<tr>
<td>Recurrence risk for:</td>
</tr>
<tr>
<td>MZ twin</td>
</tr>
<tr>
<td>Sibling</td>
</tr>
<tr>
<td>Grandchild</td>
</tr>
<tr>
<td>Cousin</td>
</tr>
<tr>
<td>Recurrence risk:</td>
</tr>
<tr>
<td>One affected 1st degree relative</td>
</tr>
<tr>
<td>Two affected 1st degree relatives</td>
</tr>
<tr>
<td>Effect of severity on risk to relatives (siblings):</td>
</tr>
<tr>
<td>Unilateral cleft lip</td>
</tr>
<tr>
<td>Bilateral cleft lip and cleft palate</td>
</tr>
</tbody>
</table>

Table 4

IV. Using the Twin Method to Analyze Human Multifactorial Traits (Supplemental Information)

A. There are two types of twins: monozygotic (MZ) which are derived from a single fertilized egg, and dizygotic (DZ) which are derived from two fertilized eggs.

1. MZ twins share 100% of their genes (G) with each other, and are assumed to share a common environment (C). Thus any phenotypic differences between MZ twins are due to differences in their individual environments (E).

2. DZ twins share 50% of their genes with each other, and are also assumed to share a common environment. So phenotypic differences between DZ twins are due to differences in their genes and in their individual environments.
3. We can use this information to estimate to what extent genes, common environment and individual environment contribute to individual differences in quantitative traits.

For MZ twins Correlation in a trait = G + C

For DZ twins Correlation in a trait = 0.5G + C

Thus (MZ correlation) - (DZ correlation) = 0.5G

So once G is estimated, both C and E can be estimated since the sum of G, C, and E must be 1 (i.e., the total variation in a trait is due to genetic, common environmental, and individual environmental differences).

4. The heritability of a trait is the proportion of variation in the trait which is due to genetic differences, i.e., G/(G+C+E). This allows us to see to what extent differences between individuals for a given trait are due to genetic differences.

KEY WORDS

Multifactorial inheritance, genetic liability, threshold model

RESOURCE


Answer to Application of Assessment of Recurrence Risk:

Non-syndromic cleft lip and palate may be considered a multifactorial trait and it occurs more frequently in men. Thus using the threshold model for multifactorial traits, the threshold is higher for affected women. Thus affected women have a higher liability and their children will be at higher risk for oral clefting. Of the children of either affected women or affected men, their sons will be at higher risk than their daughters since the threshold is lower for men.