Multifactorial Inheritance

Many disorders demonstrate familial clustering and any recognized pattern of Mendelian inheritance.

These conditions show a definite familial tendency, but the risk would be higher if these conditions were caused by mutations in single genes.

It is likely that many factors, both genetic and environmental, are involved = multifactorial inheritance

Disorders that Show Multifactorial Inheritance

**Congenital Malformations**
- Cleft lip/palate
- Congenital dislocation of the hip
- Congenital heart defects

**Acquired Diseases of Childhood and Adult Life**
- Asthma
- Autism
- Diabetes mellitus
- Epilepsy
- Glaucoma
- Hypertension
- Ischemic heart disease
- Neural tube defects
- Pyloric stenosis
- Talipes
- Manic depression
- Multiple sclerosis
- Parkinson disease
- Psoriasis
- Rheumatoid arthritis
- Schizophrenia

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Fasa University of Medical Sciences, November 2017
Multifactorial Inheritance

- Sequencing of the human genome has shown that the 3 billion base pairs are 99.9% identical in every person.
- Within that 0.1% lies the mystery of why some people are more susceptible to a particular illness, or more likely to be healthy.

Polygenic Inheritance and the Normal Distribution

- Inheritance and expression of a phenotype being determined by many genes at different loci, with each gene exerting a small additive effect.
- Show a continuous distribution in the general population, which closely resembles a normal distribution.
- It can be seen that as the number of loci increases, the distribution increasingly comes to resemble a normal curve.
**Degree of Relationship**

<table>
<thead>
<tr>
<th>Degree of Relationship</th>
<th>Proportion of genes shared</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First degree</strong></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>1/2</td>
</tr>
<tr>
<td>Siblings</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td></td>
</tr>
<tr>
<td><strong>Second degree</strong></td>
<td></td>
</tr>
<tr>
<td>Uncles and aunts</td>
<td></td>
</tr>
<tr>
<td>Nephews and nieces</td>
<td></td>
</tr>
<tr>
<td>Grandparents</td>
<td>1/4</td>
</tr>
<tr>
<td>Grandchildren</td>
<td></td>
</tr>
<tr>
<td>Half-siblings</td>
<td></td>
</tr>
<tr>
<td><strong>Third degree</strong></td>
<td></td>
</tr>
<tr>
<td>First cousins</td>
<td></td>
</tr>
<tr>
<td>Great-grandparents</td>
<td>1/8</td>
</tr>
<tr>
<td>Great-grandchildren</td>
<td></td>
</tr>
</tbody>
</table>

**The Liability/Threshold Model**

- Extend the polygenic theory for the inheritance of discontinuous multifactorial disorders.
- All of the factors which influence the development of a multifactorial disorder—genetic or environmental—can be considered as a single entity known as liability.
- To account for a discontinuous phenotype with a continuous distribution, a threshold exists above which the abnormal phenotype is expressed.
Consequences of the Liability / Threshold Model

- Provides a simple explanation for the observed patterns of familial risks in conditions.

- The incidence of the condition is greatest among relatives of the most severely affected patients, presumably because they are the most extreme deviants along the liability curve.

- For example, in cleft lip/palate the proportion of affected first-degree relatives is
  - 6% if the index patient has bilateral cleft lip and palate,
  - 2% if the index patient has a unilateral cleft lip.

- The risk is greatest among close relatives of the index case and decreases rapidly in more distant relatives.

- For example, in spina bifida the risks to first-, second-, and third-degree relatives of the index case are approximately 4%, 1%, and less than 0.5%, respectively.
Spina bifida

If there is more than one affected close relative, then the risks for other relatives are increased.

In spina bifida, if one sibling is affected the risk to the next sibling is approximately 4%; if two siblings are affected, the risk to a subsequent sibling is approximately 10%.

Consequences of the Liability/Threshold Model

If the condition is more common in one sex, then relatives of an affected individual of the less frequently affected sex will be at higher risk.

Pyloric stenosis shows a male to female ratio of 5 to 1.

The proportions of affected offspring of male index patients are 5.5% for sons and 2.4% for daughters.

Whereas the risks to the offspring of female index patients are 19.4% for sons and 7.3% for daughters.
Consequences of the Liability / Threshold Model

The risk of recurrence for first-degree relatives approximates to the square root of the general population incidence.

Thus if the incidence is 1 in 1000, the sibling and offspring risk will equal approximately 1 in 32, or 3%.

Heritability

The proportion of the total phenotypic variance of a condition that is caused by additive genetic variance

Provide an indication of the relative importance of genetic factors in its causation

Heritability is estimated from the degree of resemblance between relatives or using data on the concordance rates in monozygotic and dizygotic twins

Estimates of Heritability in Different Disease

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency (%)</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>1</td>
<td>85</td>
</tr>
<tr>
<td>Asthma</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>Cleft lip + cleft palate</td>
<td>0.1</td>
<td>76</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>0.3</td>
<td>75</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>0.2</td>
<td>70</td>
</tr>
<tr>
<td>Club foot</td>
<td>0.1</td>
<td>68</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>Hypertension (essential)</td>
<td>5</td>
<td>62</td>
</tr>
<tr>
<td>Congenital dislocation of the hip</td>
<td>0.1</td>
<td>60</td>
</tr>
<tr>
<td>Anencephaly and spina</td>
<td>0.3</td>
<td>60-bifida</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>0.5</td>
<td>35</td>
</tr>
</tbody>
</table>
Population Genetics

� Aspects of gene inheritance in a given Population

� How genes are distributed and maintained at particular frequencies in populations

� How the carrier frequency and mutation rate can be determined from the disease incidence?

� Why a particular genetic disorder can be more common in one population or than another?

Hardy-Weinberg principle

� In an ‘ideal’ population, the relative proportions of the different genotypes (and phenotypes) remain constant from one generation to another.

� An autosomal locus with two alleles, A and a, that have frequencies of p and q, respectively.

Displayed: 

\[ p + q = 1 \]

\[ p^2 + 2pq + q^2 = 1 \]

� When studies confirm that the relative proportions of each genotype remain constant with frequencies of \( p^2, 2pq, \) and \( q^2 \), then that population is said to be in Hardy-Weinberg equilibrium for that particular genotype.

Factors that Can Disturb Hardy-Weinberg Equilibrium

� 1. Non-random mating

� 2. Mutation

� 3. Selection

� 4. Small population size

� 5. Gene flow (migration)
Estimation of Carrier Frequencies

If the incidence of an AR disorder is known, it is possible to calculate the carrier frequency.

If the disease incidence is 1 in 10,000, then
\[ q^2 = \frac{1}{10,000} \text{ and } q = \frac{1}{100} \]

Because \( p + q = 1 \) therefore \( p = \frac{99}{100} \)

The carrier frequency \( 2 \times (\frac{99}{100} \times \frac{1}{100}) \) (i.e., \( 2pq \)), which approximates to 1 in 50

A rough approximation of the carrier frequency can be obtained by doubling the square root of the disease incidence.

Why Are Some Genetic Disorders More Common than Others?

Small Population
- Founder effect

Large Population
- High mutation rate
- Heterozygote advantage

Small Population

High allele frequencies are usually explained by the combination of a founder effect together with social, religious, or geographical isolation—hence the term genetic isolates.

Several very rare AR disorders in the Old Order Amish living in Pennsylvania

Founder effects can also be observed in AD disorders. Variegate porphyria, in the Afrikaner population of South Africa
Large Population

- High incidence in a large population, a very high mutation rate and/or a heterozygote advantage.

- Heterozygotes show a slight increase in biological fitness compared with unaffected homozygotes referred to as heterozygote advantage.

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<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genetics</th>
<th>Region/Population</th>
<th>Resistance or Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liddle's disease</td>
<td>AR</td>
<td>Whole of Africa</td>
<td>Familial malaria</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>AR</td>
<td>Mediterranean</td>
<td>Familial malaria</td>
</tr>
<tr>
<td>Hypertension</td>
<td>AR</td>
<td>Northern Europe</td>
<td>Familial malaria</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>AR</td>
<td>Eastern European</td>
<td>Inflammatory</td>
</tr>
<tr>
<td>Hypertension</td>
<td>AR</td>
<td>Northern Europe</td>
<td>Inflammatory</td>
</tr>
</tbody>
</table>

AR: Autosomal recessive; AD: Linked recessive; AR: autosomal dominant; CYP2D6: cytochrome P450, N-demethylases.