Applications in population genetics

Hanan Hamamy
Department of Genetic Medicine and Development
Geneva University

Training Course in Sexual and Reproductive Health Research
Geneva 2013

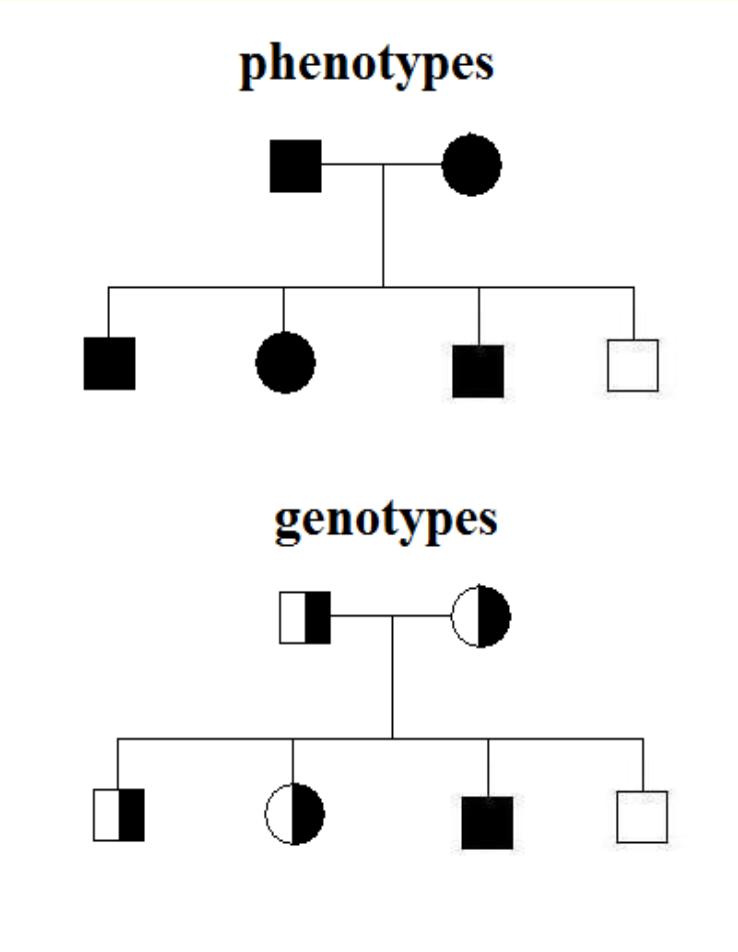
Population genetics

Population genetics involves the understanding of how genes and alleles are distributed and maintained at particular frequencies in populations.

Questions that can be answered in in accordance with the laws of population genetics

- Why a dominant trait does not increase in a population at the expense of a recessive one.
- How can the carrier frequency be determined when knowing the disease incidence.
- Why a particular genetic disorder can be more common in one population or community than in another.

Allele Frequencies in Populations



On first reflection it would be reasonable to predict that dominant genes and traits in a population would tend to increase at the expense of recessive ones.

After all, on average three-quarters of the offspring of two heterozygotes will manifest the dominant trait, but only one-quarter will have the recessive trait.

However, it can be shown that in a large randomly mating population, in which there is no disturbance by outside influences, dominant traits do not increase at the expense of recessive ones.

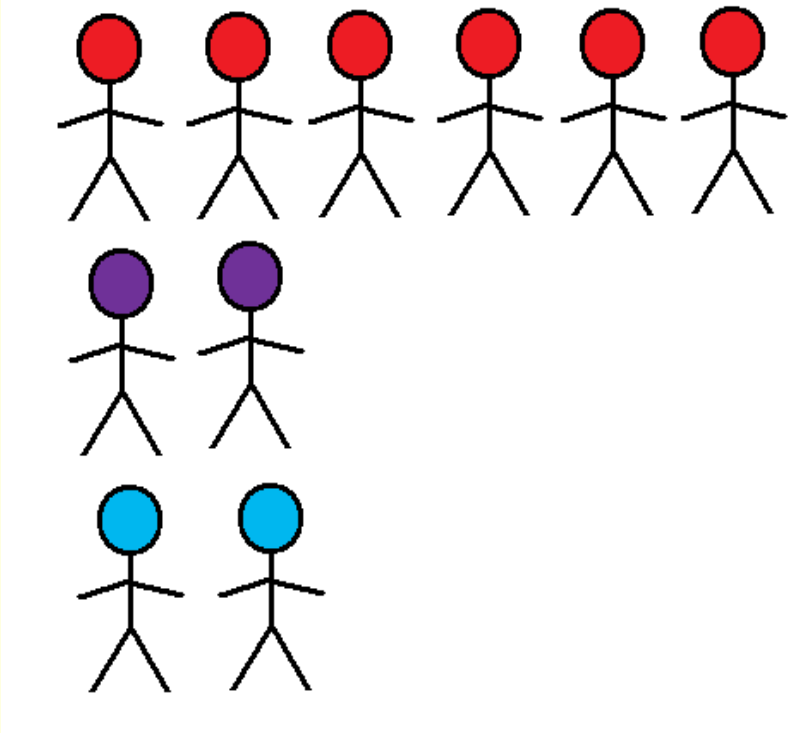
In fact, in such a population, the relative proportions of the different genotypes (and phenotypes) remain constant from one generation to another.

This is known as the **Hardy-Weinberg principle** which is one of the most important fundamental principles in human genetics.

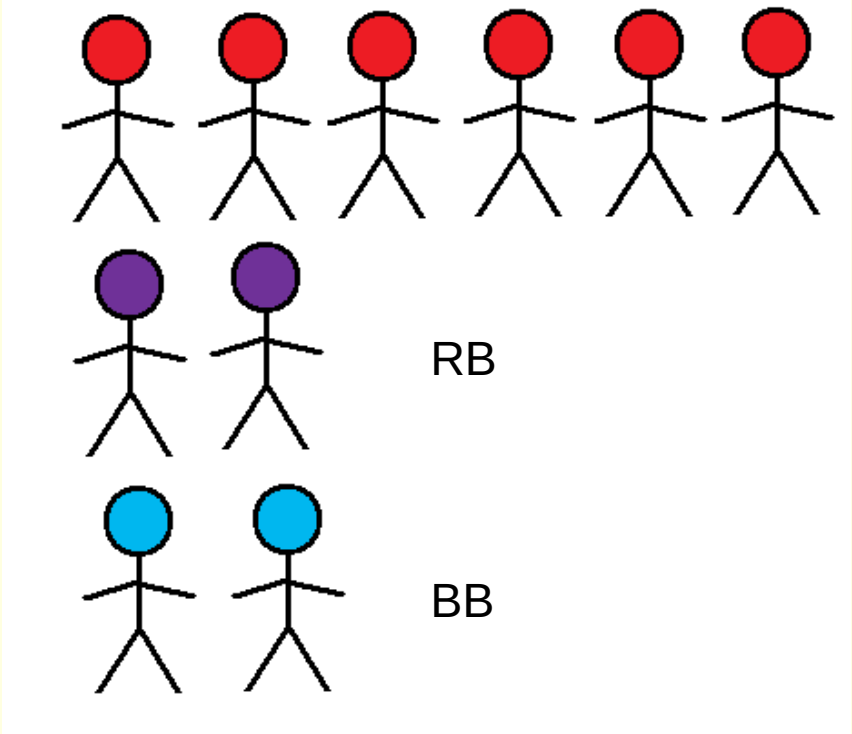
Example

In this example we have 10 persons, and 3 phenotypes: red, violet and blue.

We assume that the 3 phenotypes correspond to the 3 possible genotypes for a gene with 2 co-dominant alleles, R and B (Red and blue).



- Frequencies of genotypes:
  - RR: 6/10 60%
  - RB: 2/10 20%
  - BB: 2/10 20%
- Frequencies of alleles:
  - R: 14/20 70%
  - B: 6/20 30%



Frequency of genotypes:

Number of people with particular genotype divided by all people

Frequency of alleles (The proportion of a particular allele among all alleles at one locus in a population):

Number of particular allele divided by all people twice

Indicating allele frequencies

- If there are only two alleles, the frequency of the more frequent allele is indicated by *p,* while the frequency of the less frequent allele is indicated by *q*

p + *q* is always 1

Punnett square showing distribution of alleles when both parents are hetrozygotes:

Female gametes

	A (p)	a (q)
A (p)	AA (p2)	Aa (2pq)
a (q)	Aa (2pq)	aa (q2)

Male gametes

25% of children will be AA, 50% Aa and 25% aa

Genotype	Phenotype	Frequency
AA	A	p^2
Aa	A	2pq
aa	a	q^2

Punnett's square showing the frequencies of the different matings in the second generation

	AA (p2)	Aa (2pq)	aa (q2)
AA (p2)	p^4	$2p^3q$	p^2q^2
Aa (2pq)	$2p^3q$	$4p^2q^2$	$2pq^3$
aa (q2)	p^2q^2	$2pq^3$	q^4

Frequency of offspring

Mating type	Frequency	Frequecncy of offspring		
		AA	Aa	aa
AA X AA	p^4	p^4	-	-
AA X Aa	$4p^3q$	$2p^3q$	$2p^3q$	-
Aa X Aa	$4p^2q^2$	p^2q^2	$2p^2q^2$	p^2q^2
AA X aa	$2p^2q^2$	-	$2p^2q^2$	-
Aa X aa	$4pq^3$	-	$2pq^3$	$2pq^3$
aa X aa	q^4	-	-	q^4
Total		$P^2(p^2+ 2pq+ q^2)$	$2pq(p^2+ 2pq+ q^2)$	$q^2(p^2+ 2pq+ q^2)$
Relative frequency		P^2	$2pq$	q^2

Hardy-Weinberg principle.

- The relative frequency or proportion of each genotype is the same in the second generation as in the first.
- No matter how many generations are studied the relative frequencies will remain constant.
- The actual numbers of individuals with each genotype will change as the population size increases or decreases, but their relative frequencies or proportions remain constant.
- When studies confirm that the relative proportions of each genotype are indeed remaining constant with frequencies of p2, 2pq and q2, then that population is said to be in a state of *Hardy-Weinberg equilibrium* for that particular genotype.

FACTORS THAT CAN DISTURB HARDY-WEINBERG EQUILIBRIUM

An ideal population is large and shows random mating with no new mutations and no selection for or against any particular genotype.

Factors that disturb the Hardy-Weinberg equilibrium include:

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 autosomal recessive disorder is known, then it is possible to calculate the carrier frequency using some relatively simple algebra.

If, for example, the disease incidence equals 1 in 10000, then

$q^2 = 1/10000$ and

$q = 1/100$.

As $p + q = 1$, therefore $p = 99/100$.

The carrier frequency can then be calculated as

$2X99/100x1/100$ which approximates to 1 in 50.

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

Example

- Cystic fibrosis is an autosomal recessive disease and occurs with a frequency of 1/2500 in most Europe. What is the approximate risk of having an affected child for a couple where the man has an affected child from a previous marriage and the woman has no family history of cystic fibrosis
- 1/25
- 1/50
- 1/100
- 1/400
- 1/2500

Solution

- Since the man has a previous affected child , then he is a carrier
- The woman has no family history, and she comes from a population where the birth rate is 1 in 2500
- Thus q2 is 1/2500
- q=1/50
- Her probability of being a carrier is 2pq which is= 1/25
- The risk to have an affected child will be
- 1 (carrier status of man) X 1/25 (carrier status of woman) X 1/4 (probablity of 2 carriesr to have an affected) = 1/100

For an X-linked disorder the frequency of affected males equals the frequency of the mutant allele, q.

Red-green color blindness affects about 1 in 12 males in Western European caucasians,

$q = 1/12$ and $p = 11/12$

Frequency of affected females (q^2) =1/144

Frequency of carrier females ($2pq$) =22/144

WHY ARE SOME GENETIC DISORDERS MORE COMMON THAN OTHERS?

- Several rare autosomal recessive disorders show a relatively high incidence in certain populations and communities.
- The most likely explanation for most of these observations is that the high allele frequency has resulted from a combination of a *founder effect* coupled with social, religious or geographical isolation of the relevant group. Such groups are referred to as genetic isolates.

Heterozygote advantage

- When a serious autosomal recessive disorder, which results in reduced fitness in affected homozygotes, has a high incidence in a large population, the explanation could be the presence of heterozygote advantage

- For sickle-cell anemia and thalassemia there is good evidence that heterozygote advantage results from reduced susceptibility to *Plasmodium falciparum* malaria. The mechanism by which this is thought to occur is that the red cells of heterozygotes for sickle-cell can more effectively express malarial or altered self antigens that will result in more rapid removal of parasitized cells from the circulation.

Examples of rates of some autosomal recessive disorders

- Cystic fibrosis 1/2500
- Beta thalassemia in some countries in Middle east 1/2500
- Phenylketonuria 1/10,000

Conclusions

- According to the Hardy-Weinberg principle the relative proportions of the possible genotypes at a particular locus remain constant from one generation to the next.
- Factors which may disturb Hardy-Weinberg equilibrium are non-random mating, mutation, selection for or against a particular genotype, small population size, and migration.

Conclusions

- If an autosomal recessive disorder is in Hardy-Weinberg equilibrium the carrier frequency can be estimated by doubling the square root of the disease incidence (2pq, p very close to 1).
- Otherwise rare single-gene disorders can show a high incidence in a small population because of a founder effect coupled with genetic isolation.
- When a serious autosomal recessive disorder has a relatively high incidence in a large population this is likely to be due to heterozygote advantage.