

## Complications in single gene analysis

### A. **Lethals**

In chickens creeper X creeper  $2/3 \rightarrow$  creeper :  $1/3$  normal

But:  $1/4$ th of the eggs never hatched and were found to have grossly deformed chicks

Legend:

C'C' Lethal

C'C Creeper

CC Normal

This is often referred to as a "dominant" lethal, although in fact there is "incomplete dominance" as far as the lethal aspect of the C' allele is concerned.

Rather than being an exception as was originally considered a possibility, lethal alleles behave just as Mendel's rules predicted.

Similar examples are known in many diploid species, including flies, mice, dogs, cattle and even humans. Many "little people" are heterozygous for *achondroplasia*.

<http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?100800>

In most cases, this short-limbed form of dwarfism results from a new mutation, and by all indications, homozygosity for the defect is lethal.

**Recessive lethals** are rather common; each of us is estimated to carry recessive alleles for about 5 genes that if homozygous would be lethal, but the recessive lethals generally go unnoticed in the heterozygous condition.

The most common recessive lethal in Caucasians is "cystic fibrosis" or "CF". About 1 in 20 white's is heterozygous for the "*cftr*" gene. Homozygous individuals have salty sweat. They also have severe problems with digestion and congestion of bronchi and lungs leads to many secondary infections. Although the life expectancy has grown from 2 year to over 30 since 1940, both males and females are sterile, so the condition is still a recessive lethal. There are some indications that heterozygotes may have had an advantage in surviving diseases such as typhoid fever and cholera to account for the high frequency of the disease. Extra information can be found online at

<http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?219700>

Sickle cell anemia is a relatively common recessive lethal in blacks. It will be covered in detail later in the course.

- B. **Variable age of onset:** Another gene that can be lethal in the heterozygous condition will help us describe another problem that can make genetic analysis difficult.

Huntington disease leads to progressive degeneration of neurons and loss of muscular control, with death occurring in many cases 10-15 years after the initial diagnosis. Although anyone who inherits a defective Huntington allele can expect to eventually be affected, the age of onset varies a great deal. Less than 2% of *Hh* individuals show symptoms by age 12, the average age of onset is 38-40, but some "carriers" may not show symptoms before age 60 so may easily die from other causes. Most affected individuals survive long enough to reproduce, so in family pedigrees where the condition is present, half the children where one parent is *Hh* can expect to develop the disease.

The gene defect involved has been identified and heterozygotes can be identified. If you were at risk, would you want to know? Would your insurance company want to know?

<http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?143100>

- C. **Variable expressivity:** Just as the timing of symptoms can vary, so can the severity. In some cases, the phenotypic effects can be so great that it is difficult to realize the same gene is defective. (In fact, in many of these cases, different changes in the same gene, that is different alleles, can account for some differences in the final phenotype).

A classic example involves "osteogenesis imperfecta" in humans. In some individuals the only symptom may be blue sclera, while in others, the bones are so brittle that even walking is too much impact and leads to broken bones.

<http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?166210>

- D. **Lack of Penetrance:** Based on the previous examples, it is not surprising that in some cases, individuals known to have a particular gene from pedigree or molecular analysis do not show the expected phenotype. One common example is a dominant form of polydactyly, (extra fingers and/or toes). In addition to differences from one limb to another, some persons who pass the trait on to their offspring do not have extra fingers. In some cases, x-rays may show the extra bones were formed, but no extra digits are present.

E. **Pleiotropy**: Many genetic defects cause multiple phenotypic changes. Examples include syndromes such as that caused by a simple recessive disease called galactosemia. Individuals with galactosemia cannot digest the sugar galactose, which if untreated leads to cirrhosis and enlargement of the liver, cataracts and mental retardation.

F **Phenocopies**: Environmentally induced phenotypes can mimic genetic defects. For example, in low temperatures, flies with a gene for curly wing will have normal straight wings, and plants treated with the herbicide fluridone mimic a recessive gene that causes albinism after exposure to bright sunlight.

One of the best known phenocopies in man involves the chemical thalidomide, which is a **teratogen**.

(Teratogens interfere with normal development to cause birth defects. These defects are not the result of mutations, so will not be passed to the next generation.)

Both thalidomide and a recessive genetic condition called phocomelia result in babies born with missing limbs.

<http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?223340>

Another teratogen you may have heard of is Accutane, an effective anti-acne medicine.

G. **Genetic Heterogeneity** : Different genes may cause the same phenotype. For example, several dominant and recessive forms of polydactyly have been described, as have many genes that cause cataracts in animals or albinism in plants.

H. **Epistasis**: When just 2 genes affect the same trait we often see examples of epistasis, which is defined as one gene masking the expression of a different gene.

Note that this is not the same as dominance, where one allele masks another.

For example, consider the following hypothetical situation:

D1_ Normal	D2_ normal
d1 d1 Deaf (lacks anvils)	d2 d2 deaf (lacks stirrups)

If we cross d1 d1, D2 D2 (deaf female) X D1 D1, d2 d2 (deaf male)  
all the F1 progeny are D1 d1, D2 d2 and can hear.

Assuming that genes D1 and D2 segregate independently, intercrossing the F1 males and females should produce the classical 9:3:3:1 ratio:

9 D1_, D2_	3 D1_, d2 d2_	3 d1 d1, D2 _	1 d1 d1, d2 d2
hearing	deaf	deaf	deaf

Now there are only 2 classes of progeny, hearing and deaf, so we can't expect a 9:3:3:1 phenotypic ratio. Here d1d1 masks the expression of D2, and vice versa, so we see a 9 hearing to 7 deaf ratio.

Modified 9:3:3:1 ratios are a great clue that epistasis is involved! If 2 genes are involved the F2 dihybrid ratios will add up to 16; for example 15:1, 9:3:4, 13:3 etc. Coat colors in animals and flower colors often involve epistasis.

Other examples will be given in class and can be found in texts or on the old exams.

I **Multiple alleles**: In rabbits:

C_	brown
C <sup>ch</sup> _	chinchilla (light gray)
C <sup>h</sup> _	himalayan (black ears and paws, white body)
cc	albino

The alleles are shown in the order of dominance. In each case, a heterozygote (sometimes called a compound) will have the phenotype of the highest "ranking" allele.

Crosses between animals with different alleles often lead to new classes in the progeny, but still give 1-gene ratios.

For example  $C^{ch} C$ ,  $X C^{ch} C$  will produce 2 chinchilla: 1  
himalayan : 1 albino