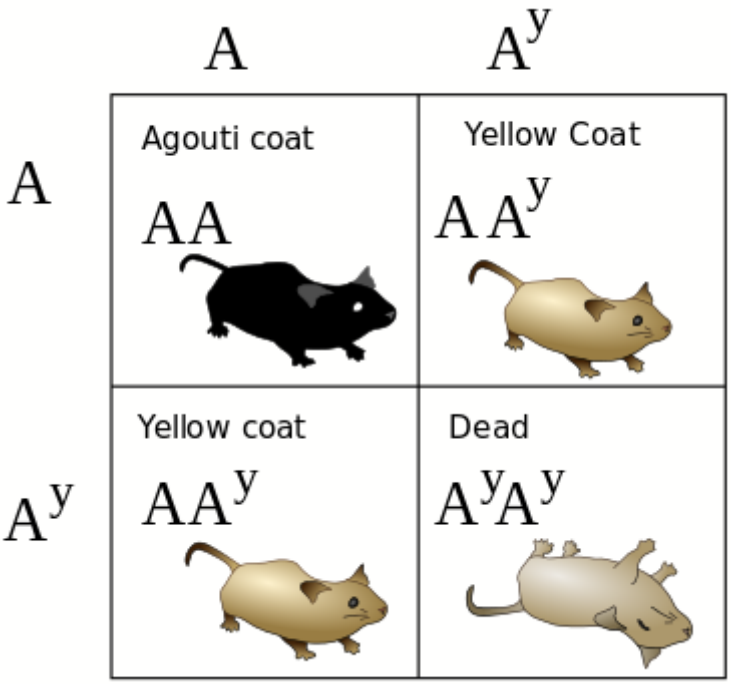
Lethal Alleles & Pleiotropism

Lethal alleles are alleles that cause the death of the organism that carries them. They are usually a result of mutations in genes that are essential for growth or development. These may be recessive, dominant, or conditional depending on the gene or genes involved. Lethal alleles can cause death of an organism prenatally or any time after birth, commonly early in development.

Lethal alleles were first discovered by Lucien Cuénot in 1905 while studying the inheritance of coat colour in mice. The agouti gene in mice is largely responsible for determining coat colour. The wild-type allele produces a blend of yellow and black pigmentation in each hair of the mouse. This yellow and black blend may be referred to as 'agouti' in colour. One of the mutant alleles of the agouti gene results in mice with a much lighter, yellowish colour. When these yellow mice were crossed with homozygous wild-type mice, a 1:1 ratio of yellow and dark grey offspring were obtained. This indicated that the yellow mutation is dominant, and all the parental yellow mice were heterozygotes for the mutant allele.

By mating two yellow mice, Cuénot expected to observe a usual 1:2:1 Mendelian ratio of homozygous agouti to heterozygous yellow to homozygous yellow. Instead, he always observed a 1:2 ratio of agouti to yellow mice. He was unable to produce any mice that were homozygous for the yellow agouti allele.



Recessive Lethals

Pair of identical alleles that are both present in an organism that ultimately results in death of that organism are referred to as recessive lethal alleles. Recessive lethals are only fatal in the homozygous condition. Heterozygotes on the other hand will sometimes display a form of diseased phenotype fore.g. achondroplasia. One mutant lethal allele can be tolerated, but having two results in death. In the case of homozygous achondroplasia, death almost

invariably occurs before birth or in the perinatal period. Not all heterozygotes for recessive lethal alleles will show a mutant phenotype, as is the case for cystic fibrosis carriers. If two cystic fibrosis carriers have children, they have a 25 percent chance of producing offspring having two copies of the lethal allele, eventually resulting in the death of the child.

Dominant Lethals

Alleles that need only be present in one copy in an organism to be fatal are referred to as dominant lethal alleles. These alleles are uncommon in populations because they usually result in the death of an organism before it can transmit its lethal allele on to its offspring. An example in humans of a dominant lethal allele is Huntington's disease, a rare neurodegenerative disorder that ultimately results in death. A person exhibits Huntington's disease when they carry a single copy of a repeat-expanded Huntington allele on chromosome 4.

Conditional Lethals

Alleles that will only be fatal in response to some environmental factor are referred to as conditional lethals. One example of a conditional lethal is favism, a sex-linked inherited condition that causes the carrier to develop hemolytic anemia when they eat fava beans.

Pleiotropism

leiotropy is the well-established phenomenon of a single gene affecting multiple traits. It has long played a central role in theoretical, experimental, and clinical research in genetics, development, molecular biology, evolution, and medicine. In recent years, genomic techniques have brought data to bear on fundamental questions about the nature and extent of pleiotropy. However, these efforts are plagued by conceptual difficulties derived from disparate meanings and interpretations of pleiotropy.

In Molecular-Gene Pleiotropy, the question is about the number of functions a molecular gene has. These functions can be defined genetically, by the number of measured traits affected by a knockout, but also biochemically, for example, by the number of protein-protein interactors a gene has or the number of reactions it catalyzes.

In Developmental Pleiotropy, mutations –not molecular genes –are the relevant units. Developmental pleiotropy is a feature of the genotype-phenotype map that defines the genetic and evolutionary autonomy of aspects of phenotype, independent of fitness. This is the mutational pleiotropy underlying the diverse manifestations of syndromic diseases, the ontogenetic pleiotropy that underlies classical questions about allometry and heterochrony, and molecular pleiotropy that underlies questions about relative importance of cis-regulatory vs. protein-coding variants.

In Selectional Pleiotropy, the question is about the number of separate components of fitness a mutation affects. In some cases, the multiple fitness components are life-history traits of a single individual, which is at the heart of the antagonistic pleiotropy model for the evolution of aging. In other cases, the mutational effects are manifest in different individuals in a population, which is the basis for sexually antagonistic pleiotropy and pleiotropic trade-offs underlying local adaptation. A key feature of selectional pleiotropy is that traits are defined by the action of selection and not by the intrinsic attributes of the organism.

Mendel noticed that the flower colors were always correlated with two other features: the color of the seed coat (covering of the seed) and the color of the axils (junctions where the leaves met the stem)

In plants with white flowers, the seed coats and axils were colorless. In plants with purple flowers, on the other hand, the seed coats were brown-gray and the axils were reddish. Thus, rather than affecting just one characteristic, the flower color gene actually affected three.

Genes like this, which control multiple, seemingly unrelated features, are said to be pleiotropic (pleio- = many, -tropic = multiple). We now know that Mendel's flower color gene specifies a protein that causes colored particles, or pigments, to be made squared. This

protein works in several different parts of the pea plant (flowers, seed coat, and leaf axils). In this way, the seemingly unrelated phenotypes can be traced back to a defect in one gene with several functions.

Another classic example of Pleiotropism is Cytoknes that play role in immune system functions. One cytokine has multiple functions and may induce proliferation of one type of cells and at the same time supress another.