LETHAL ALLELES, PENETRANCE, EXPRESSIVITY

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LETHAL ALLELES/LETHAL GENES

- Lethal, often referred to as fatal genes or lethal alleles, are alleles that cause the death of the entity that possesses them. Essentially, lethal genes are lethal to organism that carries them, with fatal referring to death. It is usually the result of gene mutations that are necessary for growth and development.
- When researching the inheritance of coat colour in mice in **1905, Lucien Cuenot** (French geneticist) became the first to uncover Lethal genes.
- Depending on the participating genes, lethal genes can be
    - Recessive Lethal
    - Dominant Lethal
    - Conditional Lethal

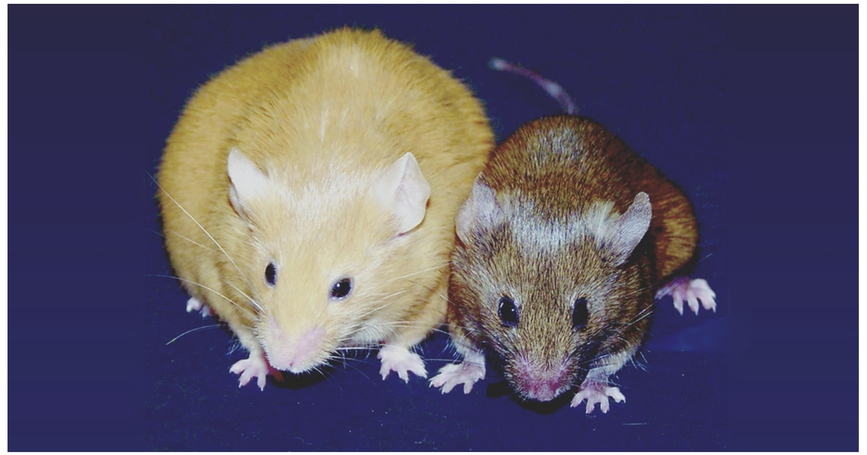
Lucien Cuenot
(1866-1951)

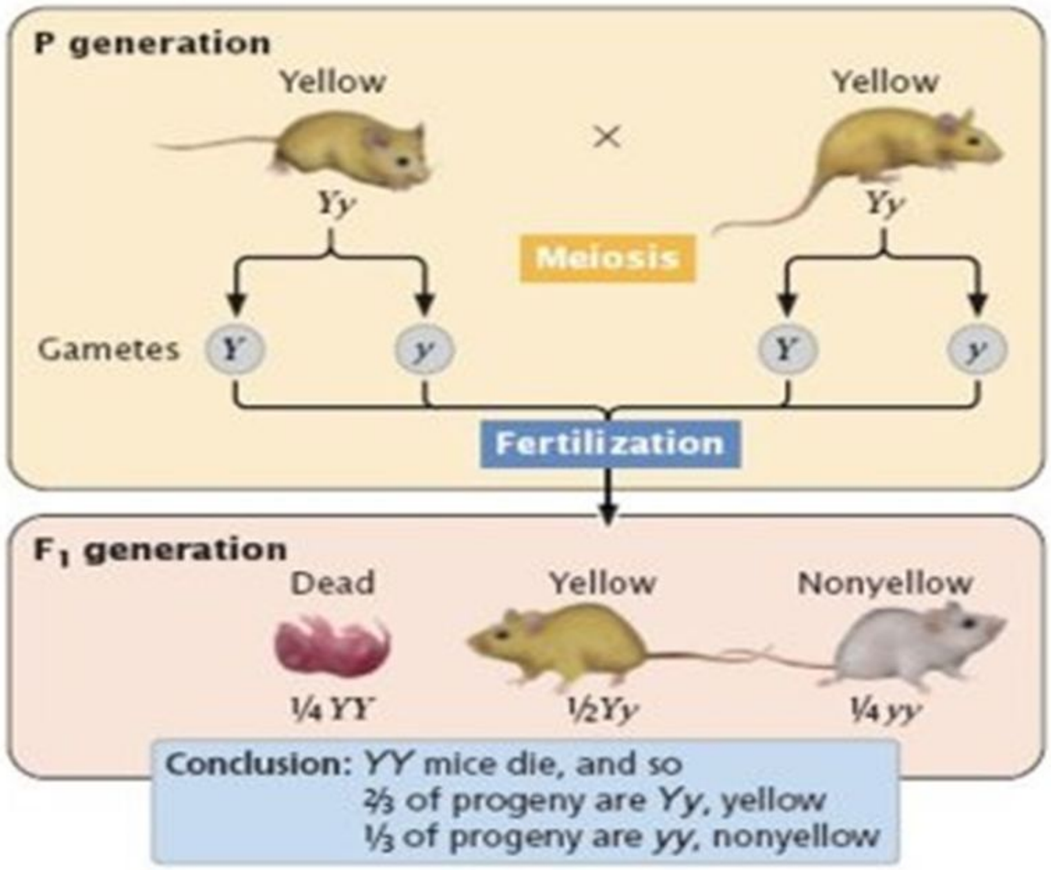
- Lucien Cuénot identified lethal alleles in 1905 while examining the inheritance of coat colour in mice.

- In mice, the agouti gene is mostly responsible for coat colour.

- The wild-type gene results in a mixture of yellow and black pigmentation in the mouse's hair. This yellow and black colour combination is known as 'agouti'. One of the agouti gene's mutant variants leads to mice that are significantly lighter and yellowish in colour.

- After mating two yellow mice, Cuénot expected to witness a typical 1:2:1 Mendelian ratio of homozygous agouti to heterozygous yellow to homozygous yellow after mating two yellow mice. Rather than that, he consistently saw a 1:2 ratio of agoutis to yellow mice. He was unable to generate any homozygous mice for the yellow agouti allele.





RECESSIVE LETHAL

- Most commonly found.
- The term recessive lethal alleles refer to a pair of identical alleles that are both present in an organism and ultimately result in the organism's death. Their expression is in homozygous conditions only, hence survival of heterozygous ones is unaffected.
- Recessive lethals can code for recessive or dominant characteristics, they turn fatal only under homozygous conditions.
- Example: Coat color in mice (discovered by Cuenot)
- Hydrocephalus in mice: In mice, hydrocephalus is due to a recessive lethal gene. In homozygotes, the gene causes abnormal growth of cartilage during embryonal development. This leads to irregularly formed skull and brain and accumulation of cerebospinal fluid. Such homozygotes do not survive, while their heterozygotes are apparently normal.

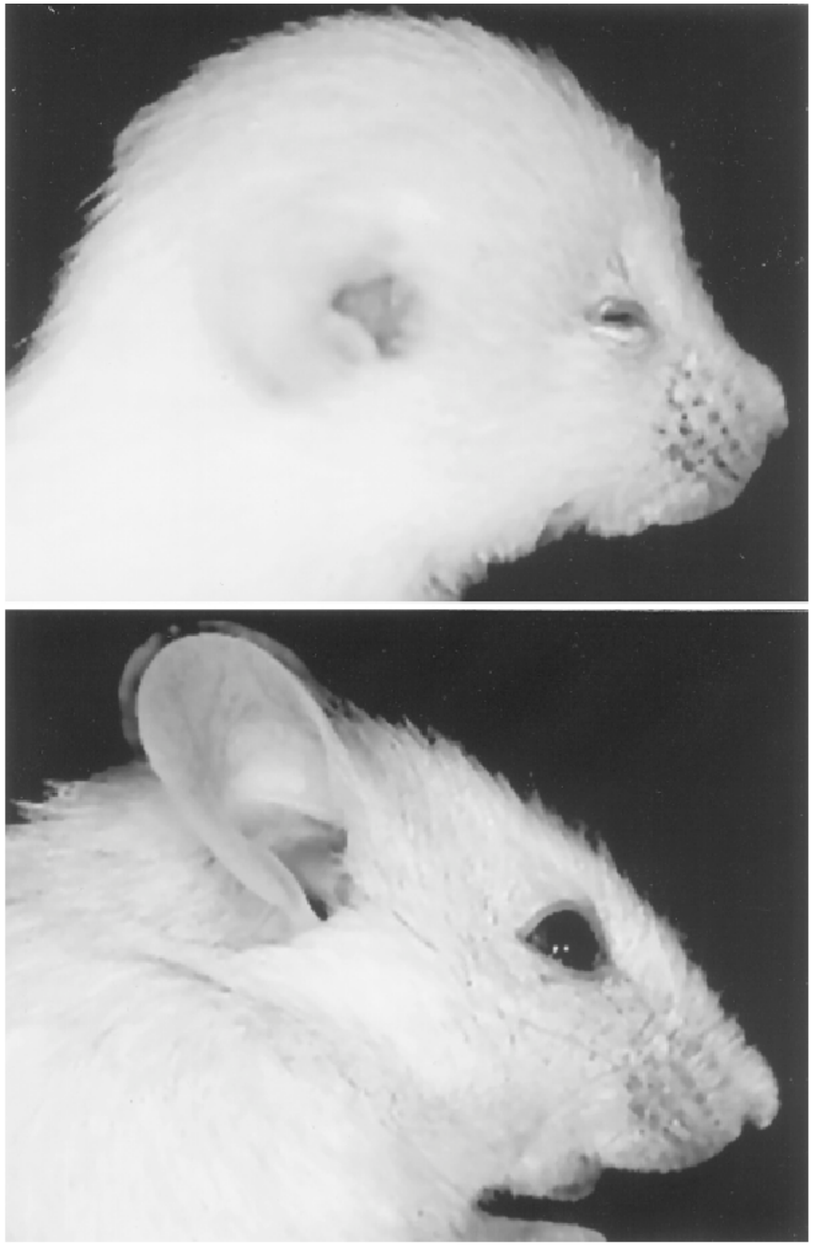


Fig: Hydrocephalus in mice

Source: Characterization of a model of hydrocephalus in transgenic mice
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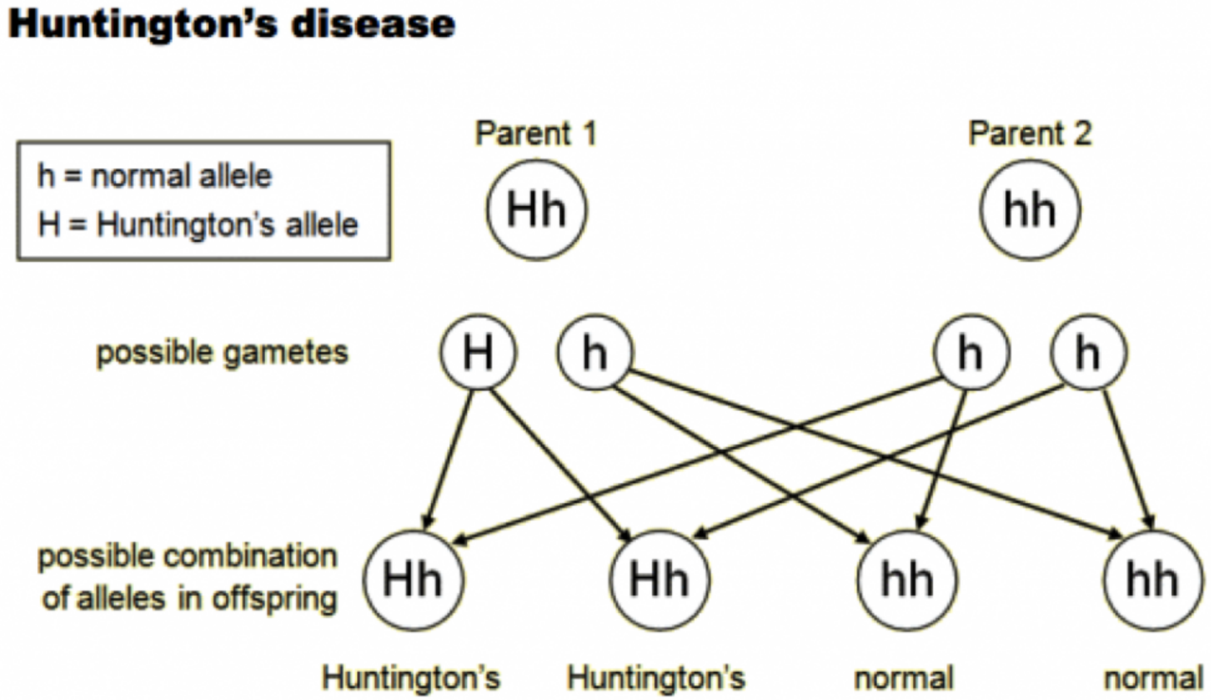
DOMINANT LETHAL

- These are the alleles whose presence is required in one copy in an entity for them to turn fatal.
- Dominant lethal genes are expressed in both homozygotes and heterozygotes.
- These are not so frequently found as they cause the death of an entity before they are transmitted to their offspring.
- Example: Huntington's disease (chorea), Epiloia (Tuberous sclerosis)
- Huntington's: In both homozygous and heterozygous condition, the gene expresses itself only at middle age, usually after forty years. The person suffers from muscular failure, mental retardation, and finally death. The gene is transmitted to next generation only because it expresses itself only after the start of reproductive period.



CONDITIONAL LETHAL

- Alleles that will only be fatal in response to some environmental factor are referred to as conditional lethals.

- Example: Favism

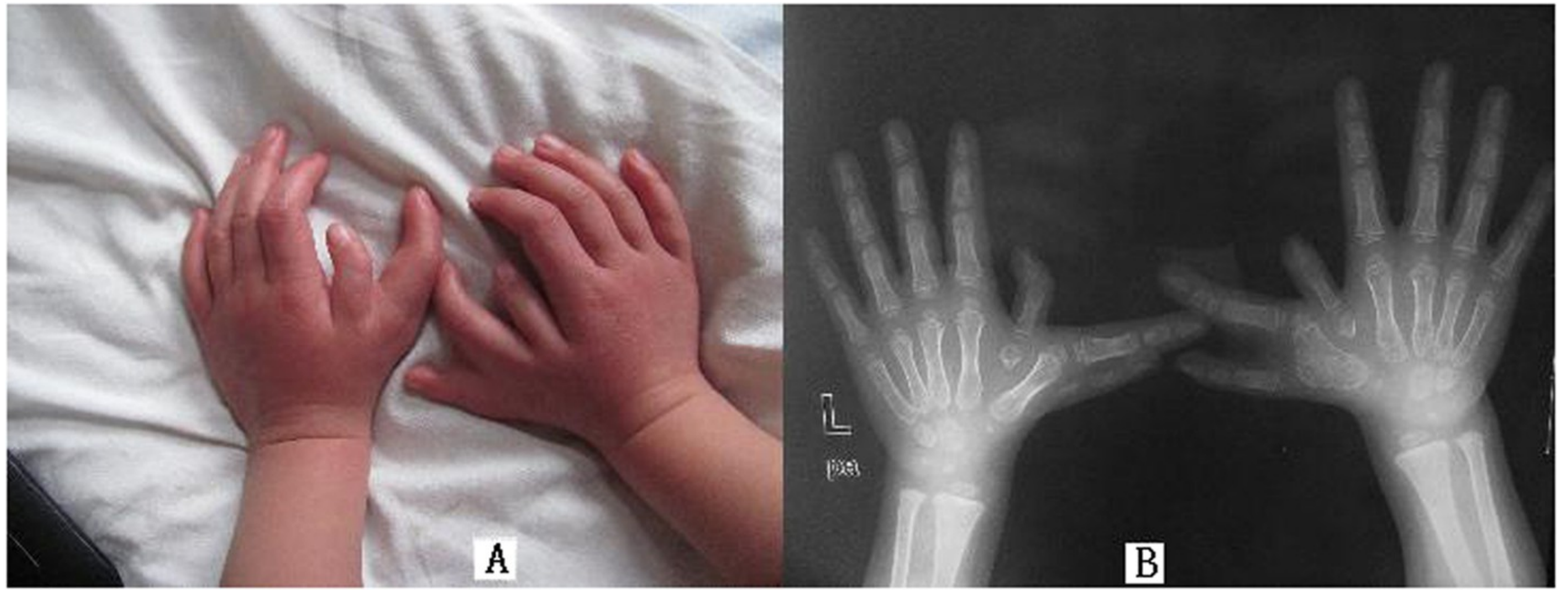
- Favism is a sex-linked, inherited condition that results from deficiency in an enzyme called glucose-6-phosphate dehydrogenase. It is most common among people of Mediterranean, African, Southeast Asian, and Sephardic Jewish descent. The disease was named because when affected individuals eat fava beans, they develop hemolytic anemia, a condition in which red blood cells break apart and block blood vessels. Blockage can cause kidney failure and result in death.

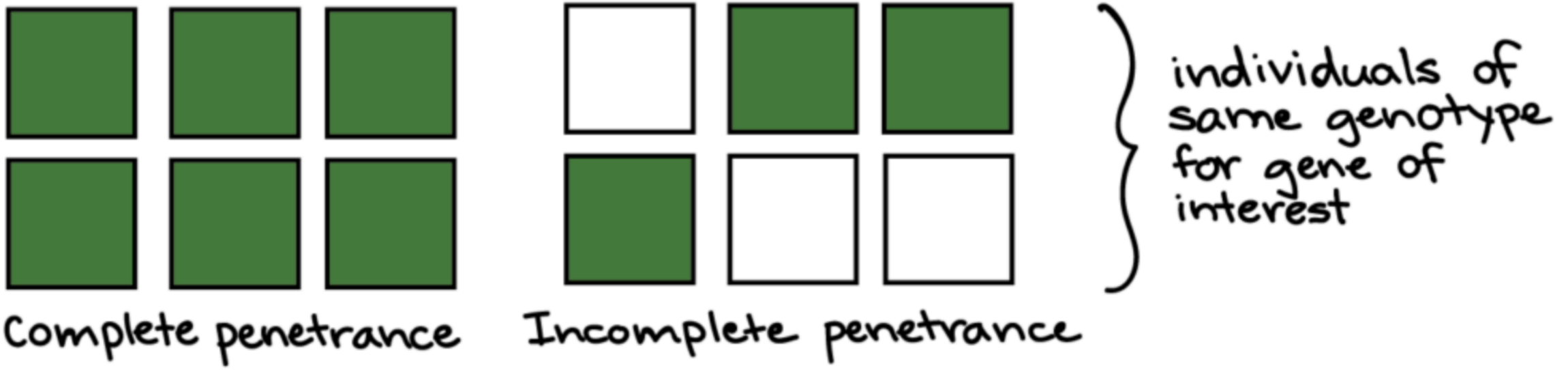
Penetrance

Penetrance refers to the proportion of people with a particular genetic variant (or gene mutation) who exhibit signs and symptoms of a genetic disorder. In some cases, despite the presence of a dominant allele, a phenotype may not be present.

Complete penetrance means the gene or genes for a trait are expressed in all the population who have the genes. **Incomplete** or ‘reduced’ penetrance means the genetic trait is expressed in only part of the population.

Example: Polydactyly in humans (extra fingers and/or toes). A dominant allele produces polydactyly in humans but not all humans with the allele display the extra digits.



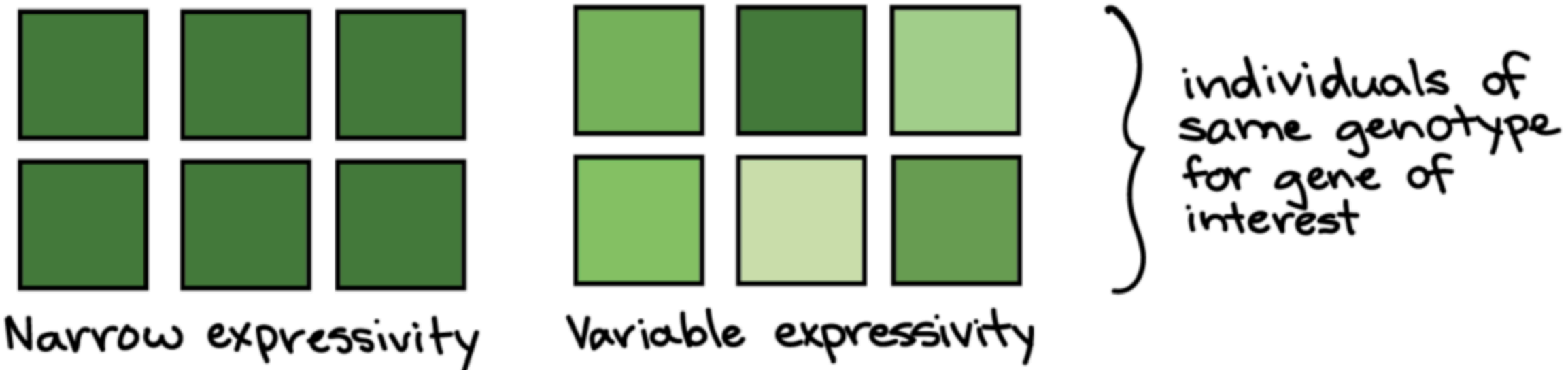

individuals of same genotype for gene of interest
Complete penetrance
Incomplete penetrance

Expressivity

Expressivity refers to variation in phenotypic expression when an allele is penetrant.

Expressivity is related to the *intensity* of a given phenotype; it differs from penetrance, which refers to the *proportion* of individuals with a particular genotype that share the same phenotype.

Variable expressivity refers to the range of signs and symptoms that can occur in different people with the same genetic condition. Variable expressivity can be seen in plants and animals, such as differences in hair colour, leaf size, and severity of diseases.



Polydactyly originates from a genetic mutation that causes cats to be born with more than the usual number of toes on their paws. While the typical cat has five toes on their front paws and four on their hind paws, polydactyl cats can have six, seven, or even more toes per paw.

A well-known example is polydactyly in Hemingway's cats, which is the presence of extra toes. The number of extra toes can differ between cats, due to variable expressivity of the *ZRS* gene.

ZRS enhances the activity of the *SHH* gene, which is involved in limb development, and this has been shown to cause extra toes.

Polydactyly in Hemingway cats