4.6: Exceptions to simple dominance

Learning Objectives

- Categorize interactions between alleles of single genes as completely dominant, incompletely dominant, or codominant and explain the biochemical basis of these relationships. Predict phenotypes of offspring using each mode of inheritance.
- Understand that multiple alleles (not just two) may exist for a gene.
- Recognize examples of incomplete penetrance, variable expressivity, and pleiotropy.
- Predict ratios of offspring when certain genotypes are lethal alleles.

Incomplete Dominance

During Mendel’s time, people believed in a concept of blending inheritance whereby offspring demonstrated intermediate phenotypes between those of the parental generation. This was refuted by Mendel’s pea experiments that illustrated a Law of Dominance. Despite this, non-Mendelian inheritance can be observed in sex-linkage and codominance where the expected ratios of phenotypes are not observed clearly. Incomplete dominance superficially resembles the idea of blending inheritance, but can still be explained using Mendel’s laws with modification. In this case, alleles do not exert full dominance and the offspring resemble a mixture of the two phenotypes.
The most obvious case of a two allele system that exhibits incomplete dominance is in the snapdragon flower. The alleles that give rise to flower coloration (Red or White) both express and the heterozygous genotype yields pink flowers. There are different ways to denote this. In this case, the superscripts of R or W refer to the red or white alleles, respectively. Since no clear dominance is in effect, using a shared letter to denote the common trait with the superscripts (or subscripts) permit for a clearer denotation of the ultimate genotype to phenotype translations.

**Exercise \( \PageIndex{1} \)**

If pink flowers arose from blending inheritance, then subsequent crosses of pink flowers with either parental strain would continue to change the phenotype. Using a Punnett Square, perform a cross between a heterozygous plant and a parental to predict the phenotypes of the offspring.

**Answer**

A cross between a heterozygote \( F^R F^W \) and a red parental \( F^R F^R \) would produce 1/2 red-flowered and 1/2 pink-flowered offspring.

\[
\begin{array}{c}
F^R \\
F^R \\
F^R \ F^R \ (red)
\end{array}
\begin{array}{c}
F^R \\
F^R \ F^R \ (red)
\end{array}
\]
Thinking about the biochemical basis of incomplete dominance

Refer back to the biochemical basis of dominant and recessive alleles. Why do many loss-of-function alleles act as recessive? What must be different about incompletely dominant alleles? How would you test your idea?

The alleles that determine curly or straight hair in dogs provide another example of incomplete dominance. Using GWAS, the KRT71 gene, which encodes a keratin protein, was identified as the locus that determines this phenotype (Cadieu et al, 2010). Dogs with C alleles for a SNP in the KRT71 gene exhibit straight hair, while dogs with curly hair have two T alleles for the SNP that alter an amino acid, which is a missense mutation. When curly and straight haired dogs are bred, such as the cross of poodles and Labrador Retrievers that create Labradoodles, the offspring are heterozygous for the SNP (C/T) and have an intermediately wavy hair.

Query \( \PageIndex{1} \)

Media, iframe, embed and object tags are not supported inside of a PDF.

---

**Codominance and Multiple Alleles**

Codominance occurs when phenotypes associated with two dominant alleles occur simultaneously. The prototypical case for this is the human ABO blood grouping. The ABO gene (also known as the I locus) on human chromosome 9 encodes a glycosyltransferase enzyme that attaches a carbohydrate molecule to proteins present on the surface of red blood cells.

The \( I^A \) and \( I^B \) alleles have several DNA sequence differences that produce amino acid changes. As a result, the \( I^A \) allele produces an enzyme that adds an acetylated galactosamine (GalNac) to a surface protein. The \( I^B \) allele produces an enzyme that adds galactose (Gal) instead. These alleles are codominant to each other because each the enzymes catalyze reactions that occur independently of the other enzymes that are present. On the surface of red blood cells in heterozygous individuals (\( I^A I^B \)), a mixture of proteins with GalNAc and Gal will be present.
A third allele of the gene, designated $i$, also exists but contains a single nucleotide deletion that causes a frameshift, completing disrupting the protein (Yamamoto et al, 1990). The protein produced by the $i$ allele does not catalyze the attachment of any sugar. This allele is recessive to $I^A$ and $I^B$ because the protein has no activity and does not influence the activity of the proteins encoded by the dominant alleles. If an $I^A$ or $I^B$ allele is also present, those enzymes will still function, so the A or B antigens will be present, producing the dominant phenotype.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I^A_-$</td>
<td>Type A</td>
</tr>
<tr>
<td>($I^A I^A$ or $I^A i$)</td>
<td></td>
</tr>
<tr>
<td>$I^B_-$</td>
<td>Type B</td>
</tr>
<tr>
<td>($I^B I^B$ or $I^B i$)</td>
<td></td>
</tr>
<tr>
<td>$ii$</td>
<td>Type o</td>
</tr>
<tr>
<td>$I^A I^B$</td>
<td>Type AB</td>
</tr>
</tbody>
</table>

Figure $\PageIndex{2}$: The three alleles of ABO system can produce 6 genotypes and four blood phenotypes: A, B, O and AB. (CC0 Wikimedia Commons)
Importance of ABO Blood Types

The alleles of the ABO gene determine features that are present on the surface of blood cells that are used when cells identify foreign cells. An individual with blood type A has proteins with the GalNac modification, but does not have proteins with the Gal modification produced by the I^B allele. The individual will produce antibodies that recognize the Gal modification that is present in Type B blood. Therefore, if Type B blood should not be introduced into a Type A individual.

Blood type influences blood donors and recipients

The table shows how blood type influences blood donations. If an individual receives a blood type that they make antibodies against, the blood will be recognized as foreign and the immune system will attack the donated cells. Because individuals will Type O blood have cells without any sugar modifications, their blood can be donated to any other blood type; they are sometimes called universal donors. In contrast, individuals with Type AB blood recognize either the GalNac or Gal modification and can receive any type of blood; they are sometimes called universal recipient.

<table>
<thead>
<tr>
<th>Blood type</th>
<th>Antibodies against:</th>
<th>Can donate blood to:</th>
<th>Can receive blood from:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>A or AB</td>
<td>A or O</td>
</tr>
<tr>
<td>B</td>
<td>A</td>
<td>B or AB</td>
<td>B or O</td>
</tr>
<tr>
<td>AB</td>
<td>none</td>
<td>AB</td>
<td>A, B, AB, or O</td>
</tr>
<tr>
<td>O</td>
<td>A and B</td>
<td>A, B, AB, or O</td>
<td>O</td>
</tr>
</tbody>
</table>

There are additional genes that influence human blood type, for example, blood type might also be described as O positive or AB negative. Whether blood type is positive or negative is determined by a second locus, the RHD gene, which encodes a surface protein called the Rh Blood Group D Antigen. As Mendelian inheritance predicts, the two genes, ABO on chromosome 9 and RHD on chromosome 1, are inherited independently during meiosis.

Penetrance and Expressivity

The terms penetrance and expressivity are also useful to describe the relationship between certain genotypes and their phenotypes.

- **Penetrance** is the proportion of individuals (usually expressed as a percentage) with a particular genotype that display a corresponding phenotype. For example, all pea plants that are homozygous for the allele for white flowers actually have white flowers, this genotype is completely penetrant. In contrast, many human genetic diseases are incompletely penetrant, because not all individuals with the disease genotype actually develop symptoms associated with the disease.
- **Expressivity** describes the variability in mutant phenotypes observed in individuals with a particular phenotype.
Many human genetic diseases provide examples of broad expressivity, because individuals with the same genotypes may vary greatly in the severity of their symptoms. Incomplete penetrance and broad expressivity are due to random chance, non-genetic (environmental), and genetic factors (mutations in other genes), although often it remains unknown which of these cause(s) are most responsible for individual phenotypes.

![Diagram showing wild type and mutant phenotypes with varying expressivity](image)

Figure 3: Relationship between penetrance and expressivity in eight individuals that all have a mutant genotype. Penetrance can be complete (all eight have the mutant phenotype) or incomplete (only some have the mutant phenotype). Among individuals with the mutant phenotype, the expressivity can be narrow (very little variation) to broad (lots of variation). (Original-Locke-CC:AN)

Example of variable penetrance and expressivity from nematodes

Mutations in the gene \textit{meg-1} in \textit{C. elegans} provide an example of variable penetrance as well as broad expressivity. This gene encodes a protein (MEG-1) that functions to establish the reproductive system in cells during early embryonic development. Mutant worms that lack \textit{meg-1} therefore produce sterile offspring. However, the sterile phenotype is not fully penetrant, approximately 20-25% of mutant offspring will be fertile, despite the lack of MEG-1. These sterile adults also exhibit variable expressivity; some sterile adults have severely-reduced germ-line development with few identifiable germ cells, whereas other sterile adults have an identifiable germ line but lack gametes.

![Diagram showing wild type and mutant phenotypes with varying expressivity](image)

Figure 4: Incomplete penetrance and variable expressivity in \textit{meg-1} mutants in nematodes. Worms with the wild-type alleles have a large u-shaped bilateral germ line (blue) that produces embryos (circles). Mutants with the genotype \textit{meg-1}(-/-), but some are fertile, illustrating in complete penetrance. Sterile worms that lack embryos can be severely-affected with few identifiable germ cells or moderately-affected with a small but identifiable number of germ cells that fails to produce gametes or embryos. (CC BY Leacock)

Data summarized from Leacock and Reinke, 2008

https://bio.libretexts.org/Courses/University_of_Arkansas_Little_Rock/Genetics_BIOL3300_(Fall_2021)/Genetics_Textbook/0… Updated: Mon, 27 Jun 2022 15:08:52 GMT
Powered by
Pleiotropy

While some genes are associated with a single trait, many genes encode proteins that function in multiple ways or are the basis for other traits. Pleiotropy occurs when a single genotype affects multiple phenotypes. For example, the human gene \textit{CFTR} is associated with the disease cystic fibrosis. However, variations in this gene are also associated with other phenotypes, such as congenital bilateral absence of the vas deferens (a feature that causes male infertility) and pancreatitis.

Pleiotropy is often observed when a gene is expressed in more than one tissue or organ. The CFTR protein plays a role in ion balance in the lungs, where lack of the protein is associated with the thick lung mucus characteristic of cystic fibrosis. However, CFTR is expressed and functions in ion balance in other tissues as well. Experiments that assay transcripts in multiple tissues, show that the CFTR mRNA is present in a number of tissues, including pancreas and testis. This expression pattern is consistent with some of the observed phenotypes that occur when CFTR is mutated.

![Figure 5](https://bio.libretexts.org/Courses/University_of_Arkansas_Little_Rock/Genetics_BIOL3300_(Fall_2021)/Genetics_Textbook/0...)

Figure 5: Expression level of CFTR in human tissues in TPM (transcripts per million) shows expression in kidney, liver, and testis in light blue, and higher expression in lung, pancreas, colon, and small intestine in dark blue (data from Lin et al 2014). (CC BY Expression Atlas update: from tissues to single cells (Nucleic Acids Research, 30 October 2019)

Lethal Alleles

Mutations that cause loss-of-function of a protein that is essential for organismal viability could result in lethality; often these alleles are recessive because the second copy of the gene will produce sufficient protein for survival. When two heterozygotes are crossed, 25% of offspring are expected to be homozygous for the lethal allele. Thus, the ratio of homozygous wild type to heterozygotes among the surviving offspring will be 2:1 and the offspring may all have the same phenotype, depending on the relationship between the two alleles.

\[
\begin{array}{c}
\text{emb}^+ / \text{emb}^- \times \text{emb}^+ / \text{emb}^- \\
\text{emb}^+ \\
\text{emb}^+ / \text{emb}^+ \\
\text{emb}^- / \text{emb}^-
\end{array}
\]
Figure \(\PageIndex{6}\): Example of a cross with an embryonic lethal allele of a gene designated \textit{emb}. The \textit{emb}^+ allele is wild type and the \textit{emb}^- allele is a recessive lethal, so those offspring will not survive, leaving a ratio of 2:1 \textit{emb}^+/\textit{emb}^- heterozygotes to \textit{emb}^+/\textit{emb}^+ homozygotes among the surviving offspring.

For some alleles, the heterozygote may have a different phenotype than the homozygote, in which case the phenotypic ratios of the progeny may differ from the expected ratios. The \textit{agouti yellow} (\textit{A}^Y) allele in mice is one example of an allele that produces a dominant yellow phenotype in heterozygotes, as well as pleiotropic effects including obesity and increased tumor incidence. Mammals typically produce two types of pigments, pheomelanin (a yellow pigment) and eumelanin (a black-brown pigment). The protein encoded by \textit{agouti} is a signaling protein that suppresses a receptor controlling eumelanin production. When agouti protein is present transiently during hair production, individual hairs have eumelanin at the base and tip with a central band of pheomelanin, giving an overall brown fur appearance. In \textit{A}/\textit{A}^Y heterozygotes \textit{agouti} is constantly expressed, suppressing eumelanin completely and the phenotype is yellow. The pleiotropic effects observed are likely due to interactions of the Agouti signaling protein with similar receptors that control weight and feeding behavior.

The \textit{A}^Y allele is lethal when homozygous due to the nature of the mutation. The \textit{A}^Y allele is a large (170kb) deletion that removes a part of an upstream gene \textit{Raly}, which stands for RNA-binding protein associated with the \textit{lethal yellow} mutation, and the \textit{agouti} promoter (Michaud et al 1993; Duhl et al 1994). Now the \textit{Raly} promoter controls the transcription of agouti, such that it is overproduced, suppressing melanin production and leading to yellow fur. Due to the size and position of the deletion, the coding sequences of the Raly protein are absent in the \textit{A}^Y allele. In heterozygous embryos a functional copy of \textit{Raly} remains, but Raly protein, which is normally expressed in early mouse embryos (preimplantation), is absent in homozygous \textit{A}^Y/\textit{A}^Y embryos. When translation of the \textit{Raly} mRNA was blocked in wild-type mouse embryos, only 4% of embryos developed to the blastocyst stage, consistent with the deletion of \textit{Raly}, and not the effect of \textit{agouti}, as the cause of the embryonic lethality (Duhl et al. 1994).
Video \(\PageIndex{1}\): The \textit{Raly} and \textit{agouti}\ genes are adjacent in the mouse genome. The \(A\) allele results in agouti protein transiently inhibiting eumelanin production producing black and yellow fur, whereas the \(A^Y\) deletion results in expanded agouti production and yellow fur as well as obesity. The deletion also removes the \textit{Raly}\ protein-coding sequence which is lethal in the homozygous state. (Images CC BY Ensembl and Jirtle and Dolinoy; Leacock)

Example \(\PageIndex{1}\)

The mouse gene \textit{Agouti} (\(A\)) influences the pattern of pigment in mouse fur. The mutant allele \(A^Y\) produces fur that is entirely yellow, instead of the wild-type pattern of black hairs with a central band of yellow pigment. However, \(A^Y/A^Y\) homozygous embryos die in early stages of development. You cross two yellow mice. What ratio of offspring genotypes and phenotypes do you expect?

\textbf{Solution}

The yellow mice must have the heterozygous genotype \(AA^Y\). The fertilized embryos will have the genotype ratio 1 \(A^Y/A^Y\) : 2 \(AA^Y\) : 1 \(AA\).

However the \(A^Y/A^Y\) embryos will not survive. The ratio of the surviving offspring will be 2 \(AA^Y\) yellow : 1 \(AA\) agouti.

\textbf{References:}


Contributors and Attributions

- Dr. Todd Nickle and Isabelle Barrette-Ng (Mount Royal University) The content on this page is licensed under CC SA 3.0 licensing guidelines.