**Gene interactions:** the collaborative efforts of two or more genes in specifying the phenotype for a specific trait.

**Terms used to specify interactions between alleles of different genes:**

- **no interaction** – independent, additive contribution to phenotype (unmodified Mendelian ratio: AaBb X AaBb → 9:3:3:1 if two genes, 2 alleles, complete dominance)
- **complementary gene action** (modified Mendelian ratio AaBb X AaBb → 9:7 if two genes, 2 alleles, complete dominance)
- **epistatic (epistasis)** (modified Mendelian ratio AaBb X AaBb → 9:4:3 for recessive epistasis, two genes, 2 alleles each, complete dominance)
- **modifier** (influences but doesn’t mask trait): morning glory
- **suppressor (suppression)** – a secondary mutation that can cancel the effects of a primary mutation, resulting in a wildtype or more wildtype phenotype
Modifier Genes

• affect phenotype generally by altering the phenotype produced by alleles of different genes
• a modifier typically has a subtle secondary effect on phenotype but there may be strong and weak modifiers
• a modifier does NOT mask the phenotype at the second gene locus in the way that an epistatic interaction would
**Gene Interactions: modifiers**

The coloration of the flowers depends on the:
- production of the appropriate anthocyanin pigments
- presence of metal ions and co-pigments
- the vacuolar pH in epidermal cells

These wild-type (b) and mutant (a) morning glories produce exactly the same anthocyanin pigment in their petals.

The phenotypic difference in the two plants is due to a single gene difference: the flower on the left has a recessive, loss-of-function mutation in a gene that codes for a Na⁺/H⁺ exchanger. This mutation results in a decrease in the vacuolar pH of epidermal cells causing the petals to appear purple rather than blue.

Allelic variations of this modifier gene shift the color from blue to purplish.

- vacuolar pH = 6.6
- vacuolar pH = 7.7
**Myo5a^d:** this modifier allele of the *Myo5* gene --aka the *dilute* gene -- lightens pigment intensity.

This gene codes for a non-muscle myosin—the mechanism of pigment dilution is not clear.
Hungry? It Could Be Biochemical

Appetite is largely controlled by a complex system of molecules that evolved over millions of years. They travel between the body and the brain, and within the brain itself.

**NEUROPEPTIDE Y**
- A protein that acts as a transmitter in the nervous system and helps stimulate food intake as well as regulate metabolic rate and fat formation.

**CCK**
- A hormone made in the stomach and intestine. It is a powerful appetite stimulant.

**PYY**
- Peptide YY3-36, or PYY, is made by cells in the intestine in response to food. It then circulates to the brain, where it switches off the urge to eat.

**LEPTIN**
- Made by fat cells. When levels are normal, people eat just enough to maintain their weight. But leptin’s absence signals the brain that the body lacks fat reserves. This can result in overeating.

How PYY Helps Control Eating

1. The arcuate nucleus in the hypothalamus receives signals from the body and determines whether food is needed. Its two types of neurons are triggered by PYY.

2. The neurons send the appropriate signal (eat or don’t eat) to the paraventricular nucleus. There, neurotransmitters for hunger or fullness are released.

3. The paraventricular nucleus sends signals giving priority either to feeding or to activities that use energy, including movement and growth.

4. Appetite is either triggered or suppressed.

**POLYPEPTIDE HORMONES**
with antagonistic activities:

SEE LEFT side of david
The ob (*obese*) gene codes for the polypeptide hormone leptin (ob* or OB = WT allele)

*Very rare, loss-of-function mutations in the obese gene have been observed in humans (pedigree at the end of the lecture) and studied in detail in mice.*
NOTE: Most obese individuals have high leptin levels but are insensitive to its effects (see X above). This so-called leptin resistance (failure to respond to leptin) in humans may be a common cause of obesity.

Figure 1. Leptin is secreted by adipocytes as a signal of fat storage. Leptin binds to the long form of the leptin receptor (LRb) in hypothalamic nuclei to increase metabolic rate and sympathetic tone and to enable the production of hormones required for thyroid function, reproductive function and growth. Leptin also acts to suppress feeding (thus reducing body weight) and the production of adrenal corticosteroids. Leptin increases the immune response, presumably by activating LRb on T cells. Leptin also increases insulin sensitivity by a poorly characterized CNS pathway as well as by the regulation of adipose mass. The poorly understood process of leptin resistance in obesity seems to selectively block the inhibition of feeding by leptin. Stimulatory pathways are in green and inhibitory pathways are in red.
Gene Interactions: suppression
Using a mouse model system to explore genetic control of body weight

Hormone called leptin informs the brain about the abundance of body fat. It promotes weight loss by
• suppressing appetite
• stimulating metabolism

ob/ob mice that are homozygous for a loss-of-function mutation in the obese gene are
• hyperphagic obese hypometabolic hypothermic
• diabetic infertile

What term can be applied to these phenotypic effects?
Neuropeptide Y is a neuromodulator implicated in the control of energy balance

- expression and release of NPY are inhibited by leptin
- Consequently NPY is elevated in ob/ob mice
- **AND** NPY administration to normal ob+ob+ mice causes an obese phenotype in these genetically wildtype mice
leptin = DON’T EAT

NPY = EAT

The effects of leptin are exerted through NPY

What happens if loss-of-function mutations in the ob and npy genes are combined together in the same animal?
triangles: $ob^+ ob^+ npy^+ npy^+$
open circles: $ob^- ob^- npy^+ npy^+$
closed circles: $ob^- ob^- npy^- npy^-$
What do you think $ob^+ob^+ npy^+ npy^+$ mice look like?

$ob^+ob^+ npy^+ npy^+$ $ob^-ob^- npy^+ npy^+$ $ob^-ob^- npy^- npy^-$

$+ = \text{wt allele} \quad - = \text{loss-of-function allele}$
Suppressor mutation: a mutation that counteracts the effects of another mutation:

\[ \text{mutant genotype} + \text{suppressor allele} = \text{wild-type} \]

A suppressor mutation may be in a different gene (extragenic) but can be in the same gene (intragenic). We will only consider extragenic mutations

An example of an extragenic suppressor mutation is when a mutation in gene B make the phenotype of gene A less mutant
Suppression:
• Mutation $a$ produces some detectable phenotype in an otherwise wildtype genetic background
• However, if there is a mutation in another gene, $b$, that reduces the effect of $a$, then $b$ is said to be a suppressor of $a$

Recessive mutant phenotype plus recessive suppressor:
\[ a^+a^+b^+b^+ = \text{wildtype} \]
\[ a a b^+b^+ \text{ or } a a b^+b = \text{mutant} \]
\[ a a b b = \text{wild-type or, at least, less mutant} \]
\[ a^+a^+b b = ? \text{ (depends)} \]
Only use the term suppressor when a mutant phenotype is partially or fully restored to wild-type by the presence of a suppressor allele.

The term *epistasis* is used in a different context and does not restore a mutant phenotype to wild-type.

Geneticist love suppressor mutations because it helps them to define gene products that interact with each other and to define players in biological systems that function in the same biochemical or regulatory pathways.
Genetic studies of suppressors have helped to identify components of regulatory pathways and to understand how the products interact with each other.

Many possibilities for complex gene interactions of all types with such complex physiological pathways

Hormones that control eating Nature 418: 595
Another molecular mechanism for suppression

Important to understand that these genetic “formalisms” reflect the complex protein interactions occurring in the cell

Suppressor studies can tell us a great deal about the genes involved in a process – especially who binds to whom…..
The obese gene codes for polypeptide hormone leptin, which acts to generally decrease appetite and increase metabolic rate:

What is the phenotype of heterozygotes for loss-of-function mutations (assume null) in the obese gene?

- At the level of the organisms these mutations are recessive in that body mass index and other measure of obesity are normal (see data next page)
- Interestingly, heterozygotes appear to have leptin levels that are similar to homozygotes for the wild-type allele: the four het parents and one het (based on DNA tests) sibling of the affected members of this family had serum leptin levels similar to homozygotes for the wild-type allele – this suggests that there may be compensatory mechanisms that increase the expression of the single wild-type allele in hets to something similar to individuals carrying two normal alleles (not known for sure)