Terms used to specify interactions between alleles of different genes:

- no interaction – independent, additive contribution to phenotype (unmodified Mendelian ratio: AaBb X AaBb $\rightarrow$ 9:3:3:1)
- complementary gene action (modified Mendelian ratio AaBb X AaBb $\rightarrow$ 9:7)
- epistatic (epistasis) (modified Mendelian ratio AaBb X AaBb $\rightarrow$ 9:4:3 for recessive epistasis)
- modifier (influences but doesn’t mask trait): see morning glory example in previous lecture
- suppressor (suppression) – a type of modifier
Researchers set out to identify the specific gene that was mutated in this family

141 members of a large consanguineous Pakistani family segregation deafness

**Black symbols:** affected individual (deaf) and by DNA tests homozygous for a mutation in the gene DFNB26

**Green symbols:** these individuals have dodged the genetical bullet: they are homozygous (by DNA tests) for the DFNB26 mutation but have normal hearing

What term is used to describe this suprising observation?
How can we explain the phenomenology that members of the same family carrying the same mutant allele can be either deaf or non-deaf?
The researcher found that all normal individuals carrying the deafness mutation \((d)\) also were heterozygous for another allelic variation \((S)\) in a different gene call DRNM1

- \(d^*d^* s^+s^+\) hearing
- \(d\ d\ s^+s^+\) deaf
- \(d\ d\ S\ s^+\) hearing
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:

$a^+ a^+ b^+ b^+ = \text{wildtype}$

$a a b^+ b^+ \text{ or } a a b^+ b = \text{mutant}$

$a a b b = \text{wild-type or, at least, less mutant}$

$a^+ a^+ b b = ? (\text{depends})$

Recessive deafness & dominant suppressor ($S$)

$d^+ d^+ s^+ s^+ \text{ normal hearing}$

$d d \ s^+ s^+ \text{ deaf}$

$d d \ S s^+ \text{ normal hearing}$

$d^+ d^+ S s^+ \text{ normal hearing}$
POLYPEPTIDE HORMONES with antagonistic activities: SEE LEFT

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.

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

   - Neurons that make you feel full.
   - Neurons that make you hungry.

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.

Source: Dr. Stephen Bloom, Imperial College London

David Rait
**Gene Interactions: suppression**
Attenuation of the obesity syndrome of ob/ob mice by the loss of neuropeptide Y

*Hormone called leptin informs the brain about the abundance of body fat:*

Leptin promotes weight loss by
- suppressing appetite
- stimulating metabolism


**leptin is a polypeptide hormone coded for by the ob (obese) gene in many mammals**

(ob\(^+\) or OB = WT allele)
The *obese* gene codes for the polypeptide hormone leptin

*Very rare, loss-of-function mutations in the obese gene have been observed in humans 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.
Using a mouse model system to explore genetic control of body weight

The *obese* gene codes for the polypeptide hormone leptin

*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 mice causes an obese phenotype in ob\+ob\+ mice
leptin = DON’T EAT

NPY = EAT

What happens if *loss-of-function* mutations in the ob and npy genes are combined together in the same animal?
A loss of function mutation in the NPY gene acts as a modifier (partial suppressor) of the ob mutation

triangles:  \( \text{ob}^+\text{ob}^+ \text{npy}^+ \text{npy}^+ \)
open circles:  \( \text{ob}^-\text{ob}^- \text{npy}^+ \text{npy}^+ \)
closed circles:  \( \text{ob}^-\text{ob}^- \text{npy}^- \text{npy}^- \)
What do you think $ob^{+}ob^{+}$ npy$^{-}$ npy$^{-}$ mice look like?
**Suppressor mutation:** a mutation that counteracts the effects of another mutation--

mutant genotype + suppressor allele = 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**

**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
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.

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…..
Recall that 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 organismic level 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)
The complicated relationship between genotype and phenotype

Figure 2: Serum leptin concentrations in Ob1 and Ob2 deviate markedly from the normal relationship between percentage body fat and serum leptin. Serum leptin concentrations were measured by radio-immunoassay in the probands, their relatives, adult and prepubertal controls. As expected, serum leptin levels in both adult and prepubertal controls correlated positively with estimates of percentage body fat. The serum leptin levels of Ob1 and Ob2 were markedly reduced, being the lowest recorded in this study at 10 and 0.7 ng/ml, respectively. Moreover, the finding of low circulating leptin in Ob1 and Ob2 represents a marked deviation from the expected relationship between percentage body fat and serum leptin. This relationship was not markedly different in the relatives who were heterozygous for the family-of-origin triad compared either to family members who were homozygous for the wild-type sequence or to unrelated control subjects.