Reading: 719-729
& lecture notes

Problem set 6

Definitions

Dominant

Recessive

Codominant
especially with molecular markers

Incompletely dominant

Definitions continued:

Penetrance: the frequency of affected individuals.

Expressivity: the severity of phenotype.

A puzzle

Mutations in *white* result in white eyes,
BUT what does the *white* gene do:
promote or inhibit red eyes.

If mutations reduce or eliminate *white* function,
then *white* involved in the production of red eyes.

If mutations increase the *white* function,
then *white* inhibits the production of red eyes.

Recessive mutations almost always reduce or eliminate gene function.

- **Hypomorphic (partial loss-of-function, weak) mutations reduce, but do not eliminate function.**
- **Amorphic (complete loss-of-function, null) mutations eliminate gene function.**
- **How do we distinguish between two classes, and ensure that the recessive mutations really reduce or eliminate, and not increase, gene function.**

We can use a set of rules defined by Hermann Muller.

1. ***white* produces eye color: the w^a allele reduces that production; *w* alleles reduce further.**
2. ***white* could inhibit eye color; the w^a allele increases the effectiveness of *white* to inhibit eye color; *w* alleles are even more efficient in inhibiting eye color.**

1. If *white* promotes eye color, and w^a reduces *white* function, then
adding copies of w^a should make the phenotype less severe.

w^a/Df(*w*) > w^a/w^a > $w^a/w^a/Dp(w^a)$
more mutant (less pigment)--------less mutant (more pigment)

2. If *white* inhibits eye color, and w^a increases *white* function, then
adding copies of w^a should make the phenotype more severe.

w^a/Df(*w*) < w^a/w^a < $w^a/w^a/Dp(w^a)$
less mutant (more pigment)--------more mutant (less pigment)

1 is the observed results.
Therefore, the *white* gene promotes red eye color,
and w^a is a hypomorphic mutation.

Amorphic mutations eliminate gene function.

w/Df = *w*/*w* = *w*/*w*/*Dp(w)*
more mutant (less pigment)------less mutant (more pigment)

Mutations can reduce function to various extents

tyrosinase
tyrosine ⟶ melanin

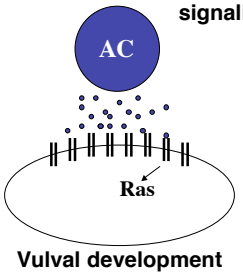
Genotype	Fur color	^{14}C-tyrosine incorporated
C^+/C^+	black	1200 +/- 36
C^+/c	black	617 +/- 33
c^{ch}/c^{ch}	grey	442 +/- 15
c^e/c^e	off white	98 +/- 11
c/c	white	47 +/- 5

$C^+ > c^{ch} > c^e > c$
an allelic series

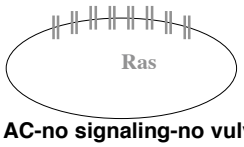
Amorphic mutations important to assess gene function.

If only had w^a hypomorphic allele, wouldn't know whether *white* gene absolutely required for pigment production; *w* amorphic alleles tells us *white* is.

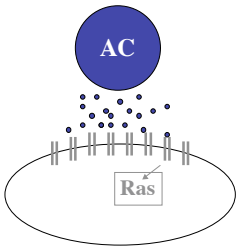
But sometimes hypomorphic alleles can give us information that null alleles cannot.
e.g., C. elegans vulva development is initiated by an EGF signal from a cell known as the anchor cell (AC) to precursor cells that generate the vulva if signaling is intact.



Vulval development



No AC-no signaling-no vulva



Hypomorphic receptor or Ras pathway mutants-no vulval development

Amorphic receptor or Ras pathway mutants die before vulval development-reveal nothing about the role of these proteins in cell signaling.

Dominant mutations can:

1. reduce gene function: haploinsufficiency

2. alter gene function: gain of function

Nail-patella syndrome is caused by haploinsufficiency of the Lmx1b transcription factor

How can we tell whether a mutation is haploinsufficient?

Df/+ = m/+

If a dominant mutation does not result in haploinsuficiency (i.e., Df/+ = m/+), then it alters gene function.

Three types of gain-of-function mutations

1. Hypermorphic mutations

2. Antimorphic mutations

3. Neomorphic mutations

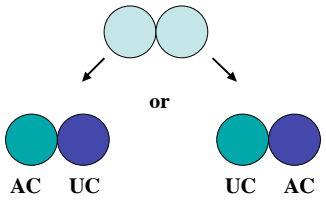
Hypermorphic mutations increase gene activity

m/+/Dp(+) > m/+ > m/Df

more mutant **less mutant**

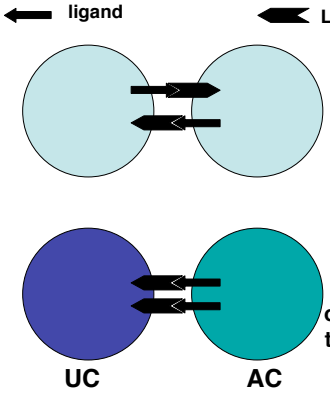
Adding wild-type alleles increases the penetrance and/or expressivity of the defect.

Cell signaling between two cells ensures that *C. elegans* hermaphrodites produce one anchor cell (AC) and one uterine cell (UC).



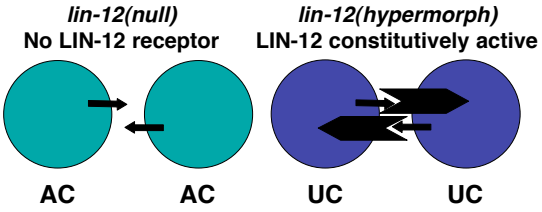
Dominant mutations in *lin-12* result in an increase in gene activity, and analysis of hypermorphmic and amorphic mutants showed that *lin-12* is a switch that controls cell fate.

genotype	Cells
lin-12(lf) / lin-12(lf)	2 ACs
lin-12(+) / lin-12(+)	AC and UC
lin-12(gf) / lin-12(gf)	2 UCs



Initially both cells express LIN-12 and its ligand

Though a feedback mechanism, only one cell expresses the ligand, and the other LIN-12.

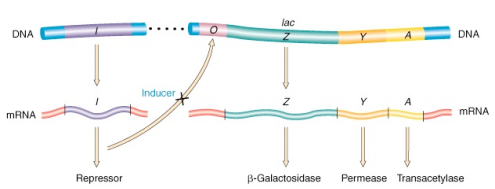


Antimorphic mutations, also known as dominant-negative mutations, antagonize wild-type gene function.

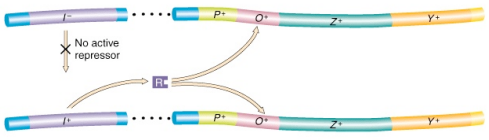
As mutant:wild-type ratio increases, mutant phenotype increases.

mutant (*m*)/wild type (+)	2:1	1:1	1:2
genotype	*m/m/Dp*(+)	*m*/+	*m*/+/*Dp*(+)
phenotype	more mutant		less mutant

The lac repressor binds to the operator of the *lac* operon to repress its transcription.



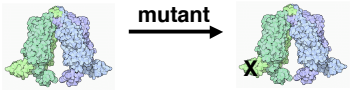
lacI$^-$ (repressor) mutations are usually recessive



The *lac* repressor is a tetramer that binds to *lac* operator. Mutations that disrupt DNA binding can be antimorphic.

Wild-type tetramer

Mutant tetramer



Binds operator

Doesn't bind operator

Neomorphic mutations result in a novel function. Dose of wild-type has no effect on phenotype.

Antp^{Ns} / Df = Antp^{Ns} / + = Antp^{Ns} / + /Dp(+)

Antp homebox gene required for leg development in Drosophila.

Antp^{Ns} **is a neomorphic mutation that results in expression of Antp from a transposable element in antennae.**