

Genetic Analysis: Our Goal

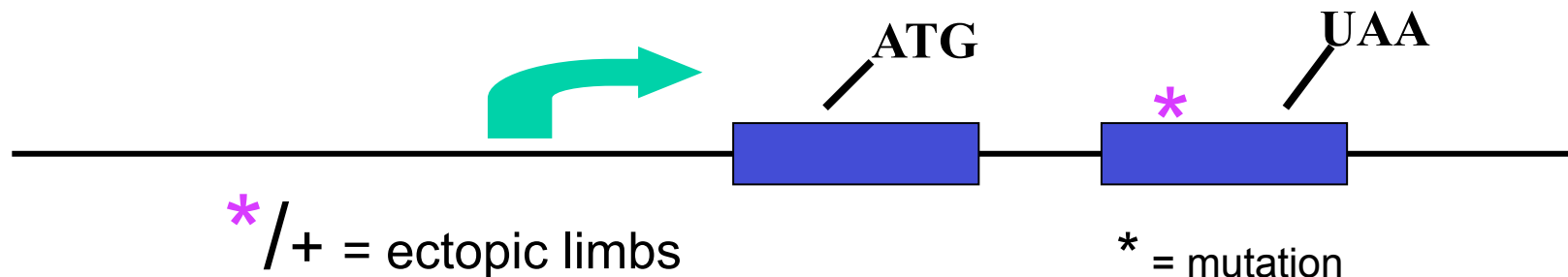
Understand a biological process

By understanding the **alteration/defect**
caused by mutations in single genes

AND

putting them in the context of other genes
with similar mutant defects

Genetic Terminology



Recessive - Dominant

$*/*$, mutant phenotype - $*/+$, mutant phenotype
 $*/+$, wild type phenotype

Haploinsufficient--

$*/+$, mutant phenotype; lof mutation
1/2 the normal dose is not sufficient for normal development

Allelism - Complementation

Amorphic/Null or Hypomorphic--

Hypomorph: $*/null > */*$, w.r.t strength of mutant phenotype
 $*/null < */*$, w.r.t. activity of gene product

Null---no functional gene product

How define a Null allele?

-- $*/Deficiency = */*$

Beware of stop codons!

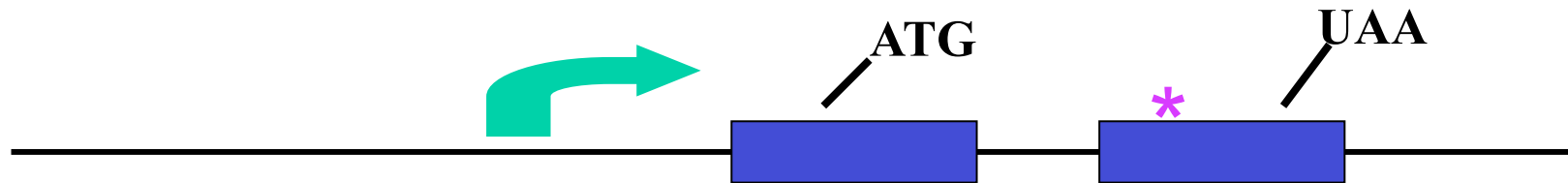
loss-of-function (lof)--

* causes reduction in activity of gene product

Hypermorphic/ Gain of function--

gof $*/+$, often opposite phenotype to **lof** $*/lof*$. Can be overexpression, overactivity, or unregulated activity of gene product.

Genetic Terminology: Epistasis



* / + = ectopic limbs, we'll call it *leggy* (constitutive activity)

How do the 3 recessive limbless genes, *als* (*alimbs*), *ton* (*trunk only*), *lls* (*lost limbs*) relate to each other and * / + (*leggy*)?

Which acts upstream and downstream of the other? How test?

Epistasis Test--Make double mutants

---in a double mutant animal,

Which ones?

mutation of one gene (the epistatic one)

masks the mutant phenotype of a second gene

Gene Order?

*als/als; * / +*

*ton/ton; * / +*

mutants must have opposite phenotypes to each other to

? limbless gene ectopic limbs?

If *als/als; * / +* has no limbs then *leggy* phenotype depends on *als*; *als* is downstream of *leggy*,
leggy -----> *als*

If *ton/ton; * / +* has ectopic limbs, then *leggy* phenotype does NOT depend on *ton* and thus *ton* is either upstream of *leggy*, *ton*-----> *leggy* OR in a parallel pathway to *leggy*.

These epistasis results are consistent with the pathway: *ton*-----> *leggy* -----> *als*

Genetic Terminology: Epistasis (another example)

Recessive mutant gene *extra limbs*, *xlb*, with ectopic limbs (similar to *leggy*).
Where does it act relative to other genes, *als*, *ton*, *lls*, and *leggy*?

Epistasis Test--Make double mutants

Which ones?

als / als ; *xlb / xlb*

ton / ton ; *xlb / xlb*

lls / lls ; *xlb / xlb*

?limbless or ectopic limbs?

Genes acting *antagonistically*
to each other

Gene Order?

If limbless phenotype, then *als* phenotype does NOT depend on wild type gene product of *xlb*,
so *xlb* is NOT downstream of *als*. The epistasis result is consistent with *xlb* -----| *als*

If ectopic limbs, then *xlb* phenotype does NOT depend on *als*, thus *als* is NOT downstream of *xlb*.

Epistasis consistent with *als* -----| *xlb*

Molecular Epistasis

Does the expression of *llb* (*limbless*) depend on *ton* or *als*?

Can decipher gene order for genes with same phenotypes.

Examples of epistasis:

Can we infer Biochemical Interactions from this Gene Order?

NO

It provides a molecular FRAMEWORK,

Potentially a pathway of genes acting in a process

Genetics does NOT replace Biochemistry

AND

Biochemistry does NOT replace Genetics

A Few more genetic terms

Penetrance --- for a given genotype, the proportion of individuals that exhibit a phenotype. **Incomplete v. Complete?**

Expressivity --- the range of phenotypes observed for a given genotype

Antimorph (genetic) / Dominant Negative (misexpression)

--- the mutant gene product is **antagonistic** to wild type activity; often dominant, but can be recessive.

$*/+$ versus $null/+$ = ?? phenotype

$*/+ > null*/+$, w.r.t strength of mutant phenotype

$*/+ < null*/+$, w.r.t. activity of gene product

Temperature-sensitive--- less activity at higher temp.,
more gene activity at lower temp.
Why useful?

Maternally expressed gene-- a gene expressed in the oocyte and
persisting in the egg, which
may function in embryogenesis

Maternal effect mutation---
genotype of mother is cause of embryonic phenotype;
genotype of father/ progeny irrelevant;
the maternally expressed gene functions in embryonic development.

Maternal-zygotic (MZ) mutation---
genotype of mother AND zygote is cause of embryonic phenotype;
a maternally and zygotically expressed gene functioning in embryonic development