

**Dominant or recessive
correlates with mutation type most times**



Hermann Muller



Muller's morphs - gene dosage tests

Loss of gene function (LoF)	amorph, nullomorph
Reduction of gene function (RoF)	hypomorph
Gain of gene function (GoF)	hypermorph
Altered function	neomorph, antimorph

m = mutation of gene

△ = deletion of gene

+ = normal allele of gene

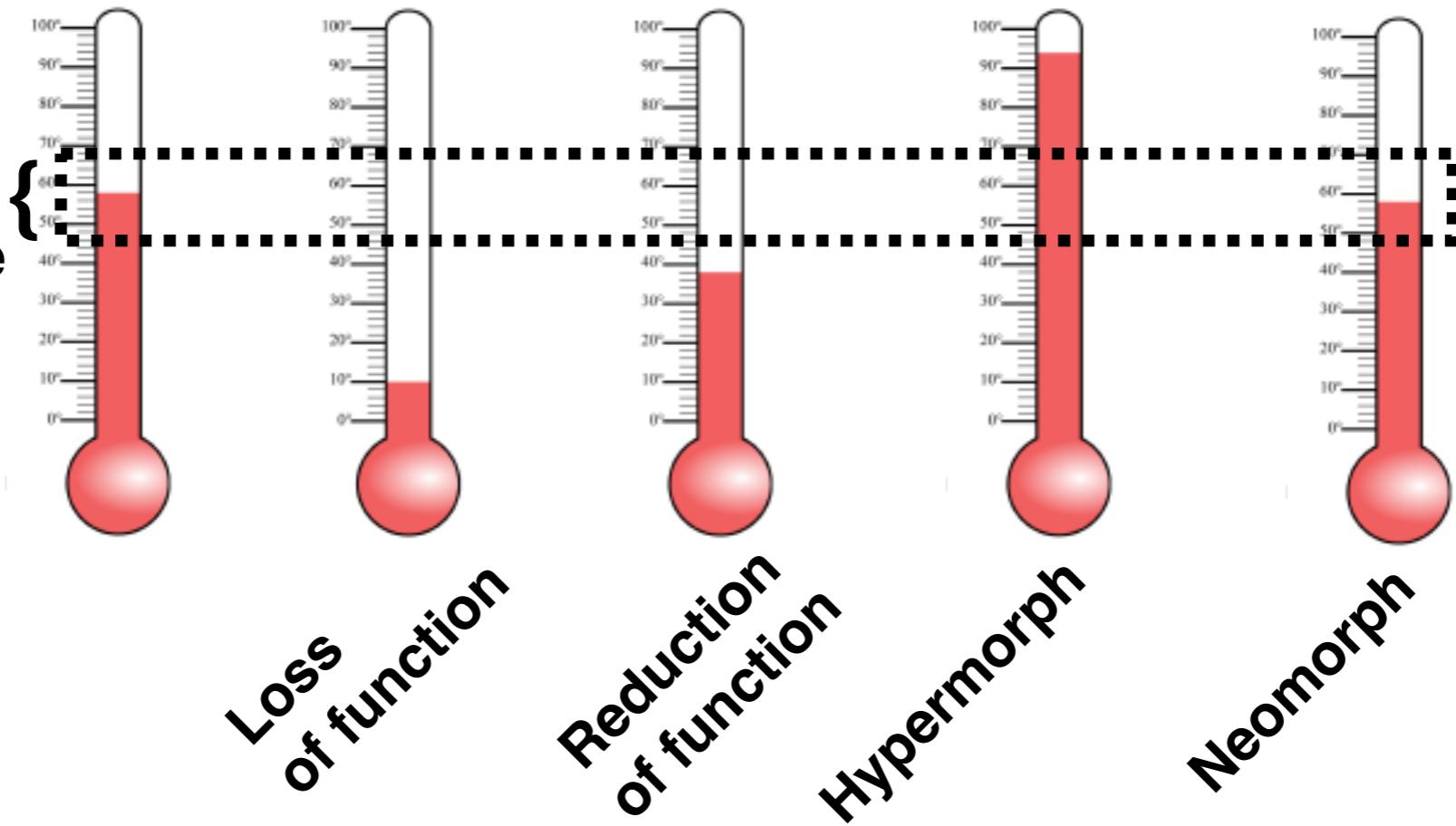
= = Phenotype is equivalent

> = Phenotype is more mutant than

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A wild-type phenotype is a reading of the amount of gene function

Range of gene function that confers a wild-type phenotype



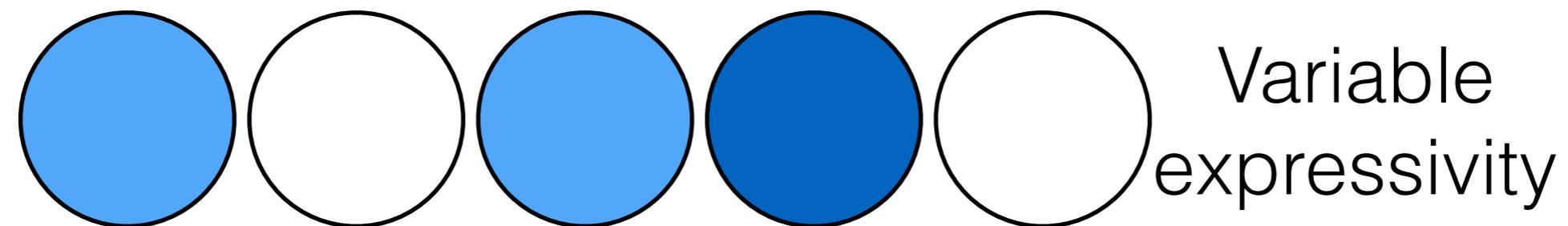
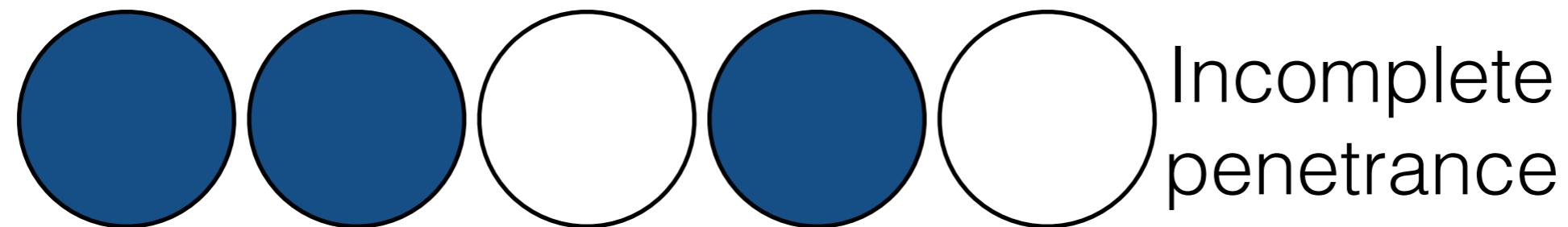
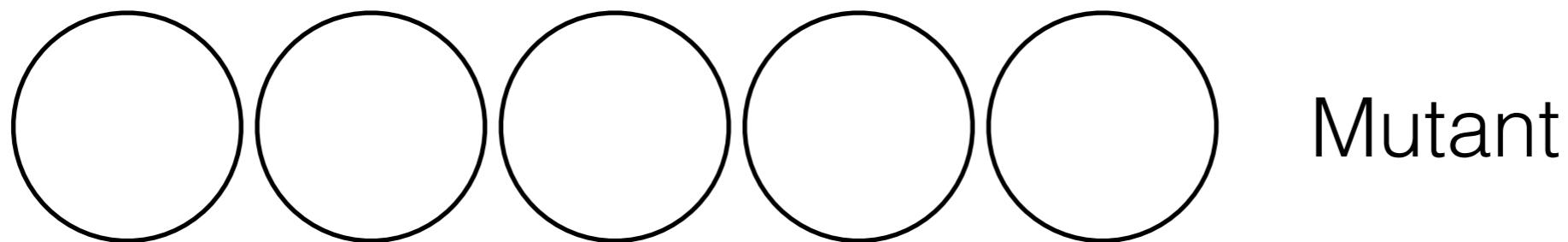
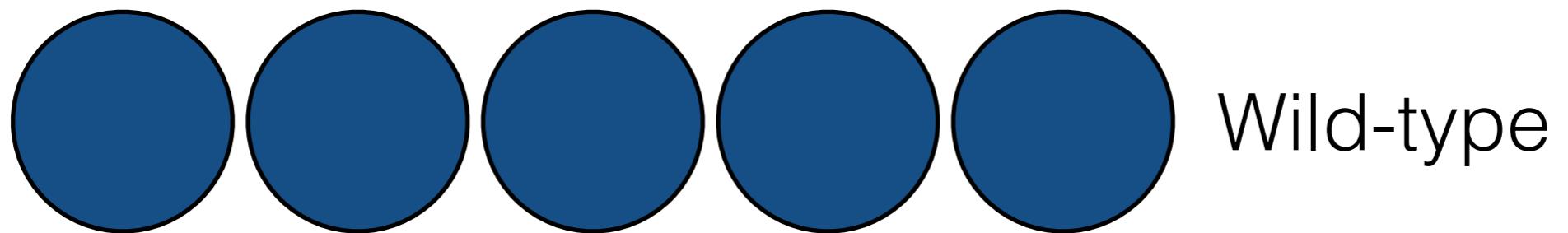
How do you get strains that are more or less mutant?

Incomplete penetrance

Even when a mutant has the mutant allele, it expresses the wild-type phenotype.

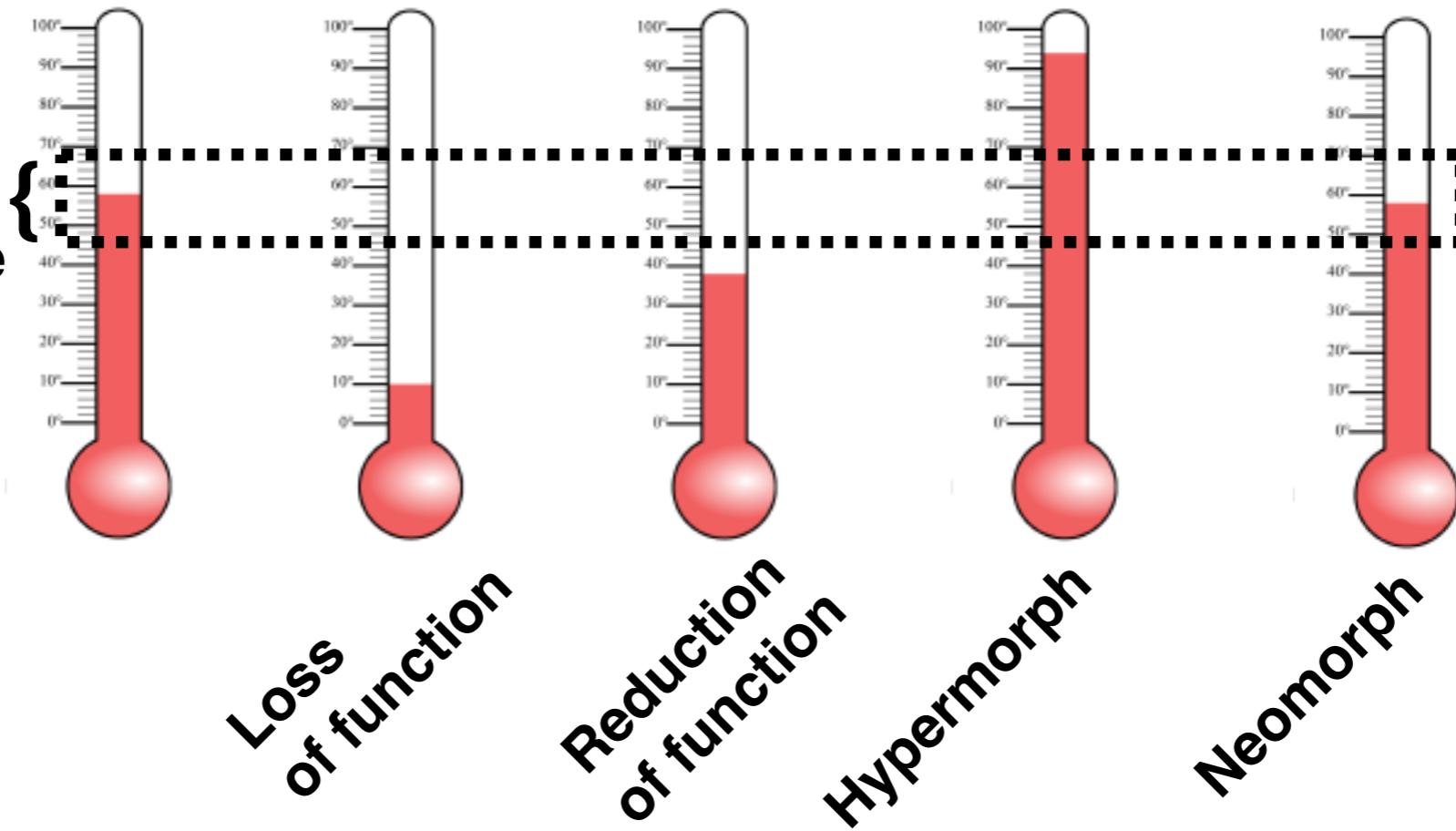
Variable expressivity

If the mutant expresses the mutant phenotype, the severity of the mutant phenotype differs from individual to individual.



A wild-type phenotype is a reading of the amount of normal gene function

Range of gene function that confers a wild-type phenotype





Wild-type worms have one vulva



Multivulva mutant worms have multiple vulvae

Incomplete penetrance is when not every mutant animal has the mutant phenotype

117/129 animals are multivulva
91% penetrant



Wild-type worms have one vulva



Multivulva mutant worms have multiple vulvae

Variable expressivity is when each mutant animal is not completely mutant

A mutant only has two extra vulvae instead of three.

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Recessive mutant phenotypes

$$\frac{m}{m} > \frac{m}{+} = \frac{+}{+}$$

amorph, *null*, or *nullamorph* = mutant causes a complete loss of gene function

$$\frac{m}{m} = \frac{m}{\Delta} > \frac{m}{+} = \frac{\Delta}{+} = \frac{+}{+}$$

hypomorph = mutant causes a partial loss of gene function

$$\frac{m}{\Delta} > \frac{m}{m} > \frac{m}{+} = \frac{\Delta}{+} = \frac{+}{+}$$

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Muller's morphs - gene dosage tests

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Dominant mutant phenotypes

$$\frac{m}{m} \geq \frac{m}{+} > \frac{+}{+}$$

haploinsufficient = two wild-type copies are required for normal function

$$\frac{\Delta}{+} \geq \frac{m}{+} > \frac{+}{+}$$

m = mutation of gene

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Muller's morphs - gene dosage tests

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Dominant mutant phenotypes

$$\frac{m}{m} \geq \frac{m}{+} > \frac{+}{+}$$

hypermorph = mutant causes an increase in wild-type function

$$\frac{m}{m} > \frac{m}{+} > \frac{m}{+} ? \frac{+}{+} > \frac{+}{+}$$

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Δ = deletion of gene

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Hypermorphic mutations cause an increase of wild-type function



Wild-type



Too much signaling

Muller's morphs - gene dosage tests

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Dominant mutant phenotypes

$$\frac{m}{m} \geq \frac{m}{+} > \frac{+}{+}$$

neomorph = mutant causes function unrelated to normal gene function (abnormal function)

$$\frac{m}{m} \geq \frac{m}{+} = \frac{m}{\Delta} = \frac{m}{\begin{matrix} + \\ - \end{matrix}}$$

m = mutation of gene

Δ = deletion of gene

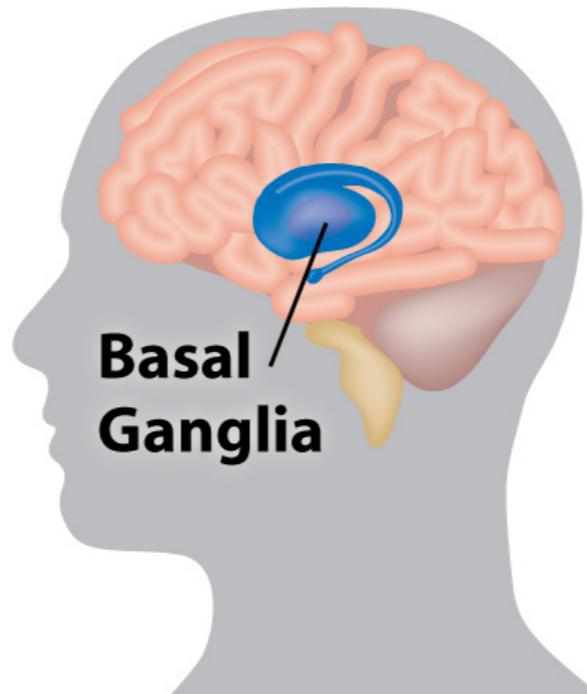
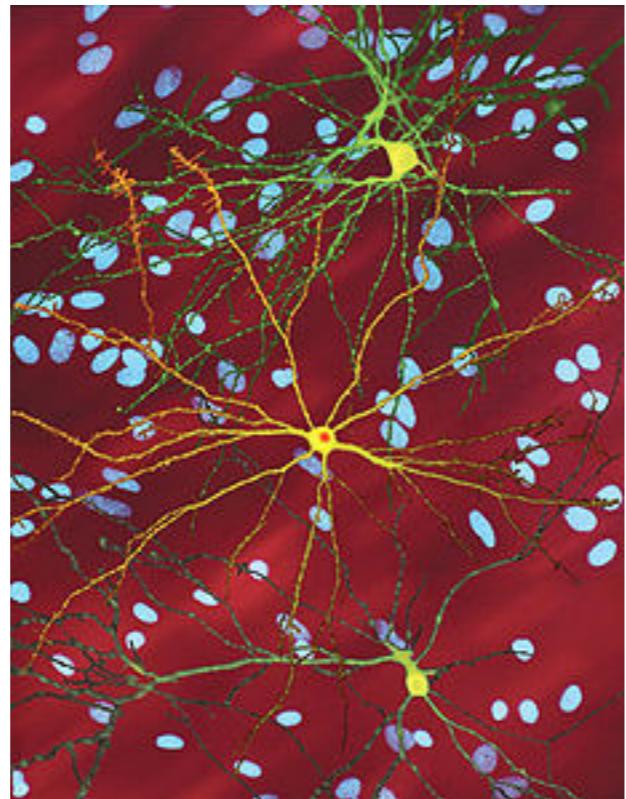
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Huntington's disease is caused by a neomorphic gain of function



The pathogenic increase in glutamine repeats causes protein aggregation. This phenomenon has nothing to do with normal protein function.

Dominant mutant phenotypes

$$\frac{m}{m} \geq \frac{m}{+} > \frac{+}{+}$$

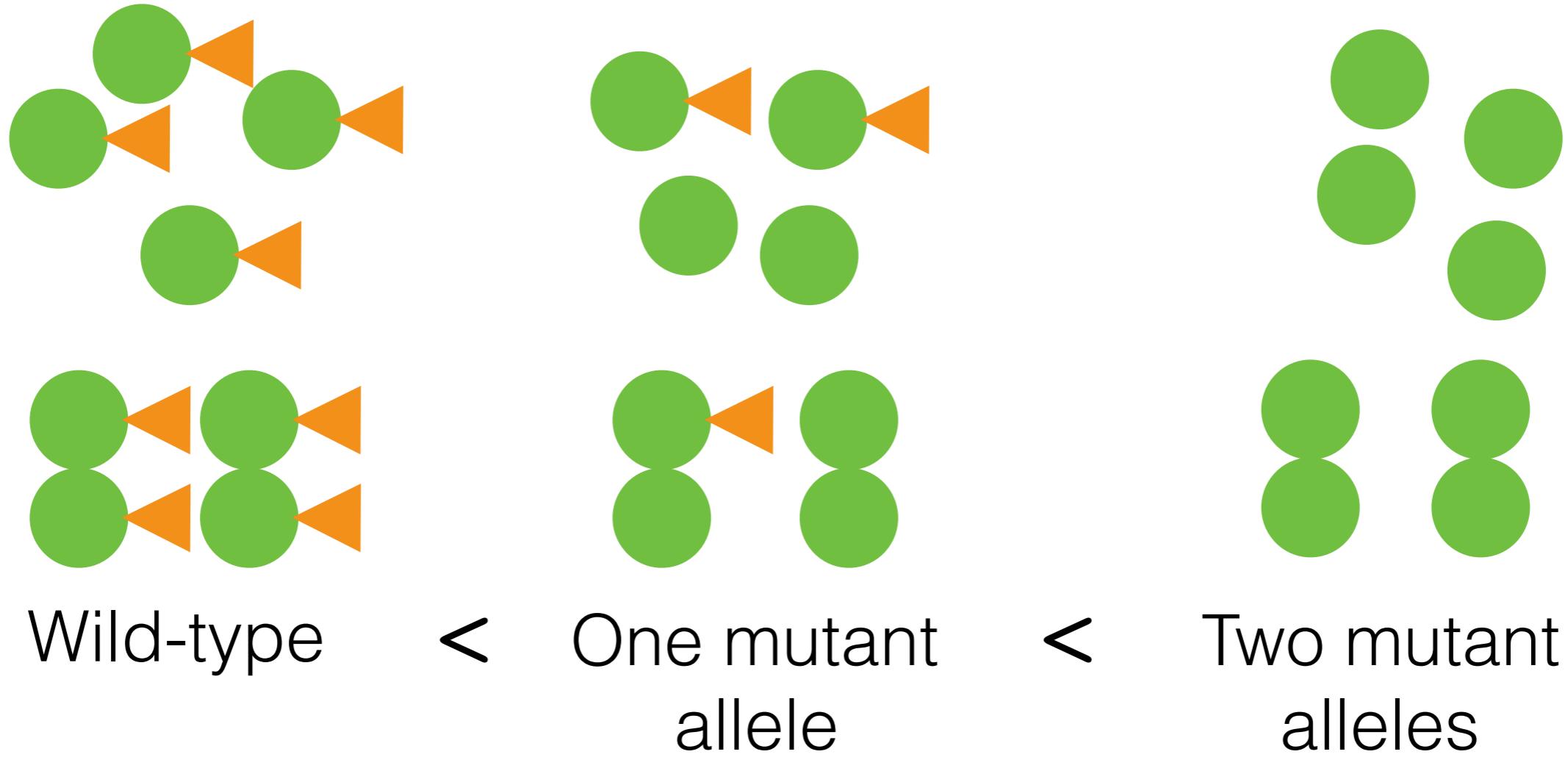
antimorph = mutant causes dominant loss of gene function
dominant negative

$$\frac{m}{+} < \frac{m}{+} < \frac{m}{m} \leq \frac{m}{\Delta}$$

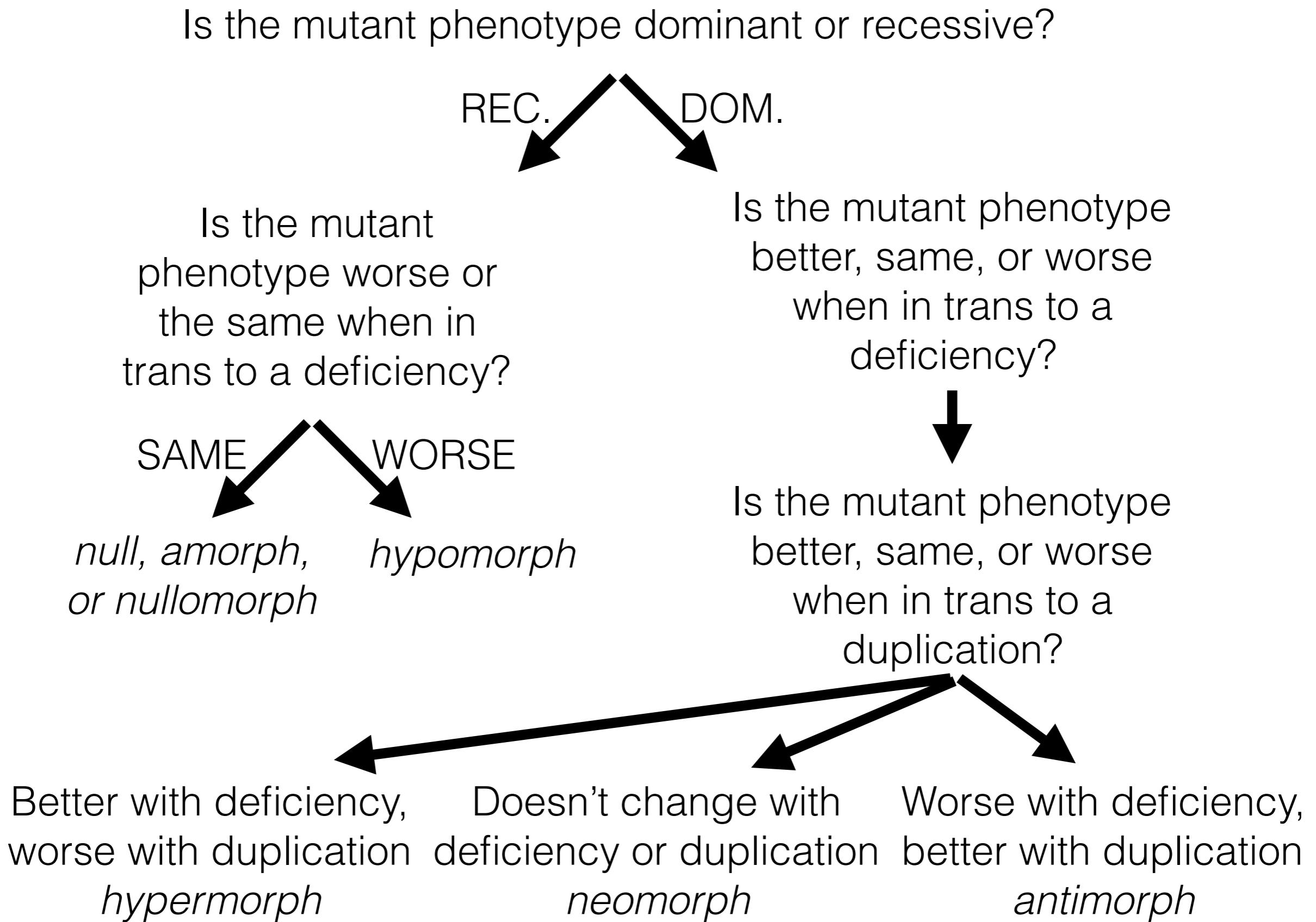
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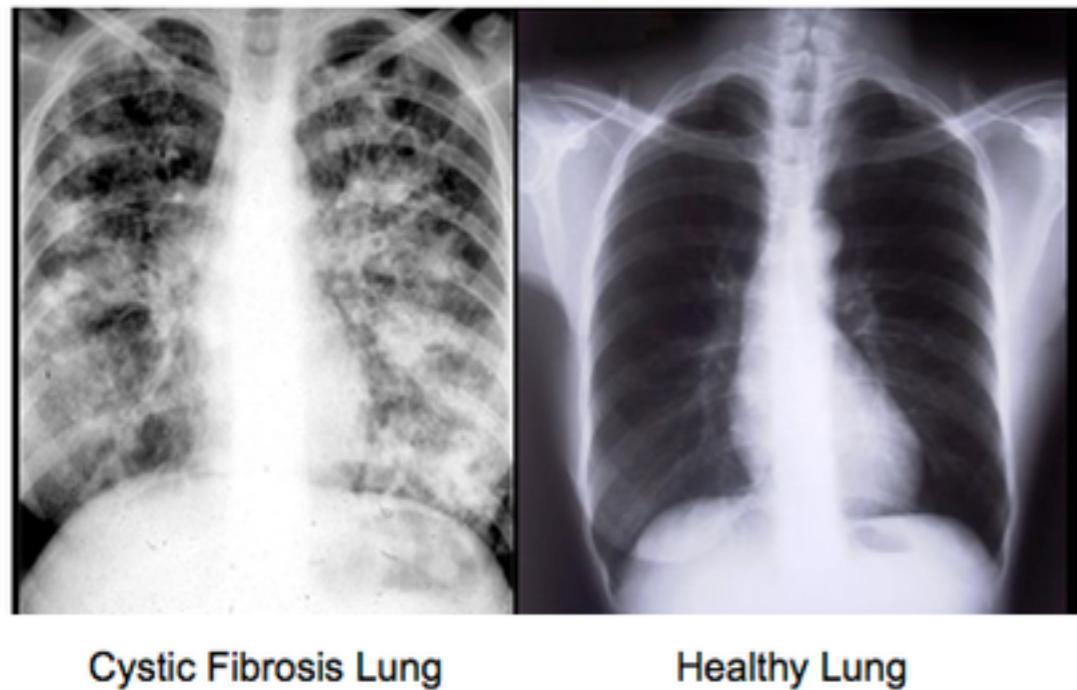
Antimorphs or dominant negatives compete with wild-type function



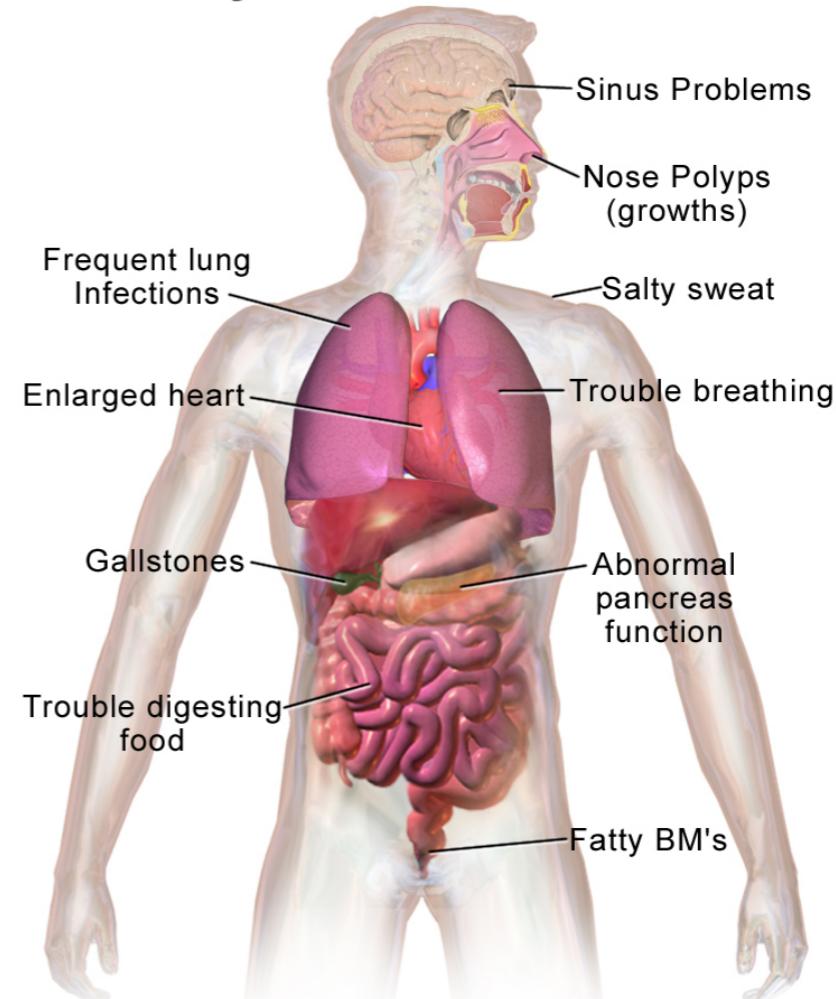
Flow chart for gene dosage studies



What about cystic fibrosis and today's topic?

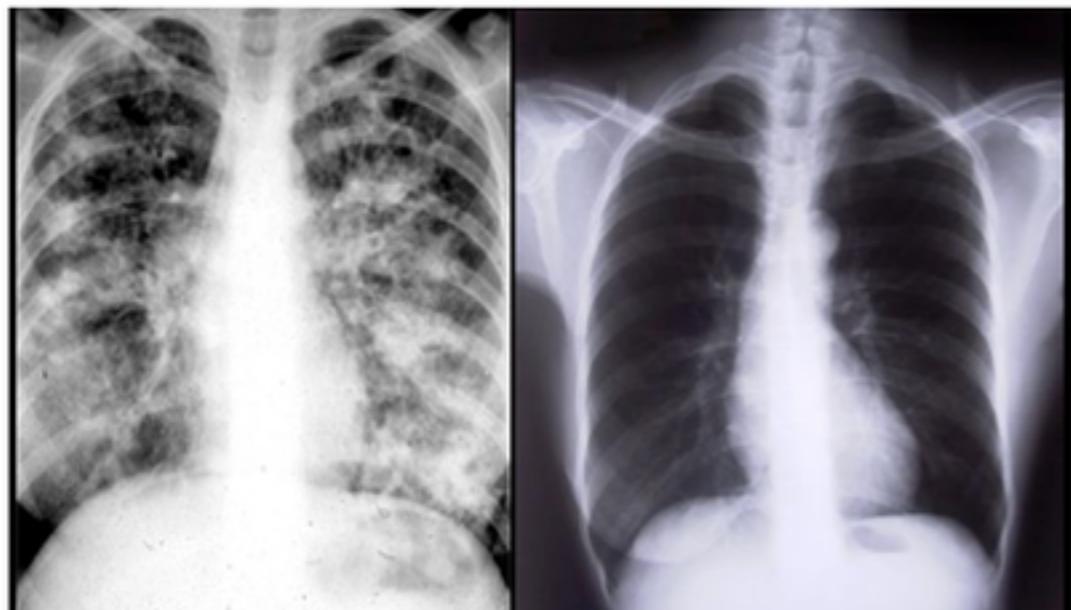


Health Problems with Cystic Fibrosis



1. Autosomal recessive disorder
2. Not caused by chromosomal aberrations or meiotic NDJ
3. Mapped to chromosome 7

CF is an autosomal recessive disorder



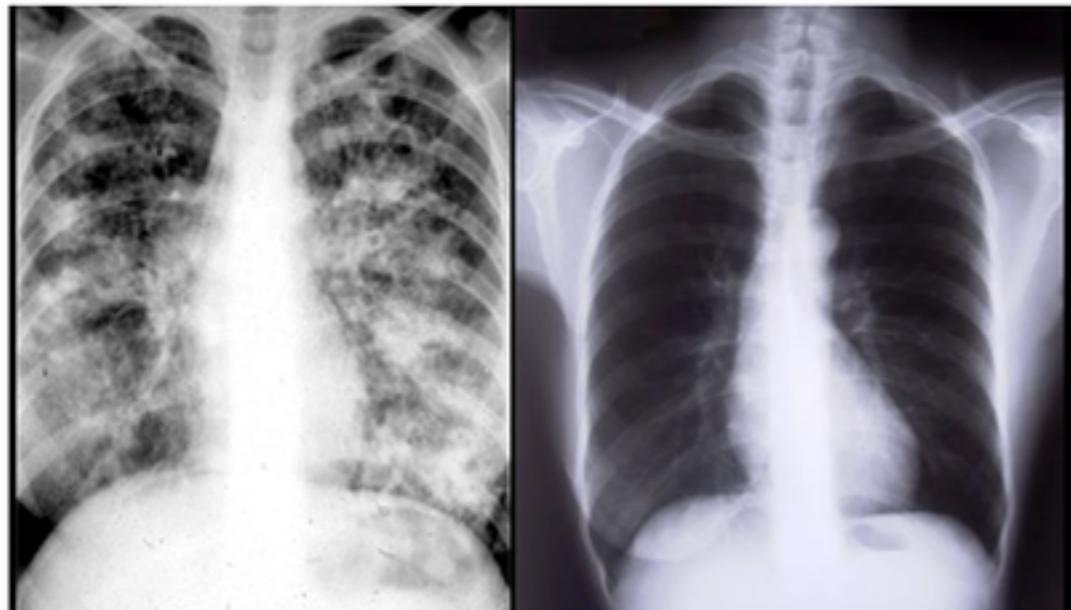
null or hypomorph?

Cystic Fibrosis Lung

Healthy Lung

CF allele	Severity	Survival (yrs)	Prevalence in pop.
F508del	High	36.3	~83%
G542X	High	36.3	~5%
I507del	High	36.3	~0.8%
R347P	Medium	50.0	~0.6%

CF is an autosomal recessive disorder



Cystic Fibrosis Lung

Healthy Lung

null or hypomorph?

How do we do gene dosage tests in humans?

Gene dosage and Complementation



Lexus CT 200h





Lexus CT 200h mutant 1
Can't drive, doesn't start



Lexus CT 200h mutant 2
Can't drive, engine dies

Complementation: a test of gene function



Lexus CT 200h mutant 1
Can't drive, doesn't start



Lexus CT 200h mutant 2
Can't drive, engine dies

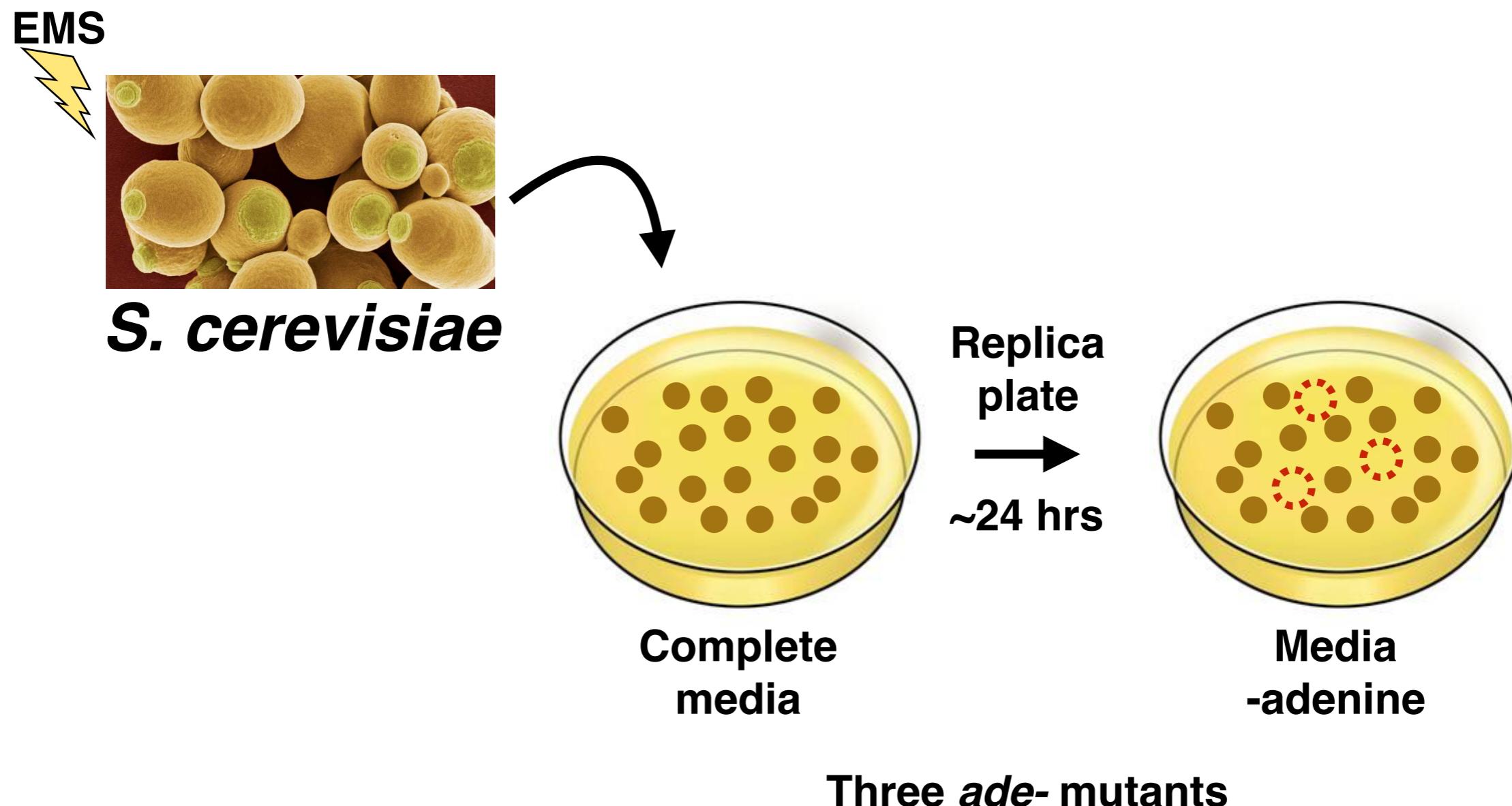
“Cross” the two mutants and get what?

What is the trait we are testing?



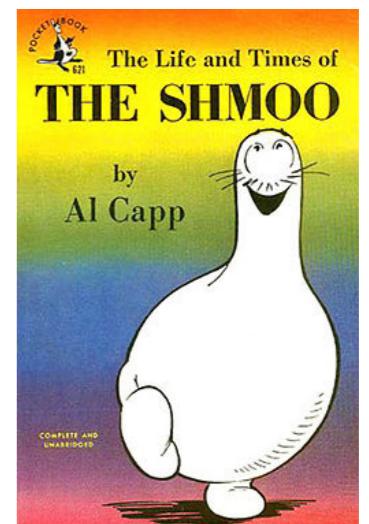
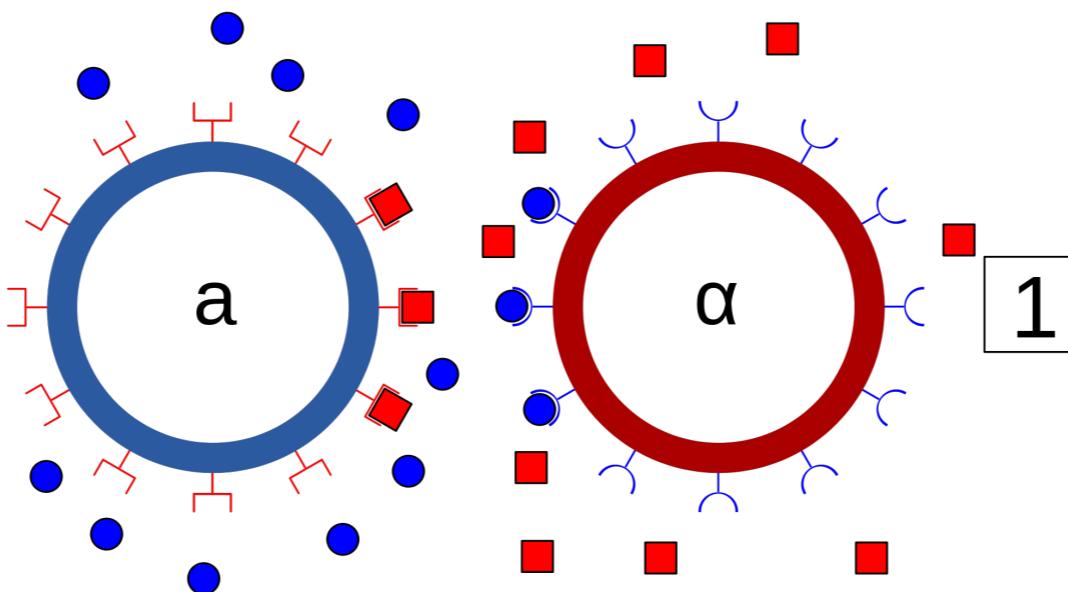
Screen for mutants that require adenine to grow

Screen:

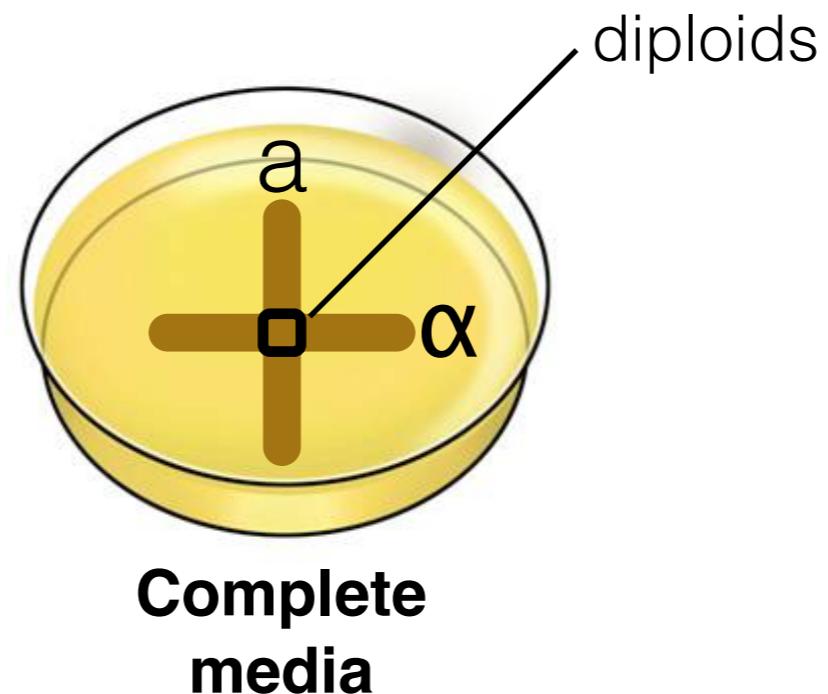


Are all three mutants deficient in the same function
(i.e. mutants in the same gene)?

Yeast mating



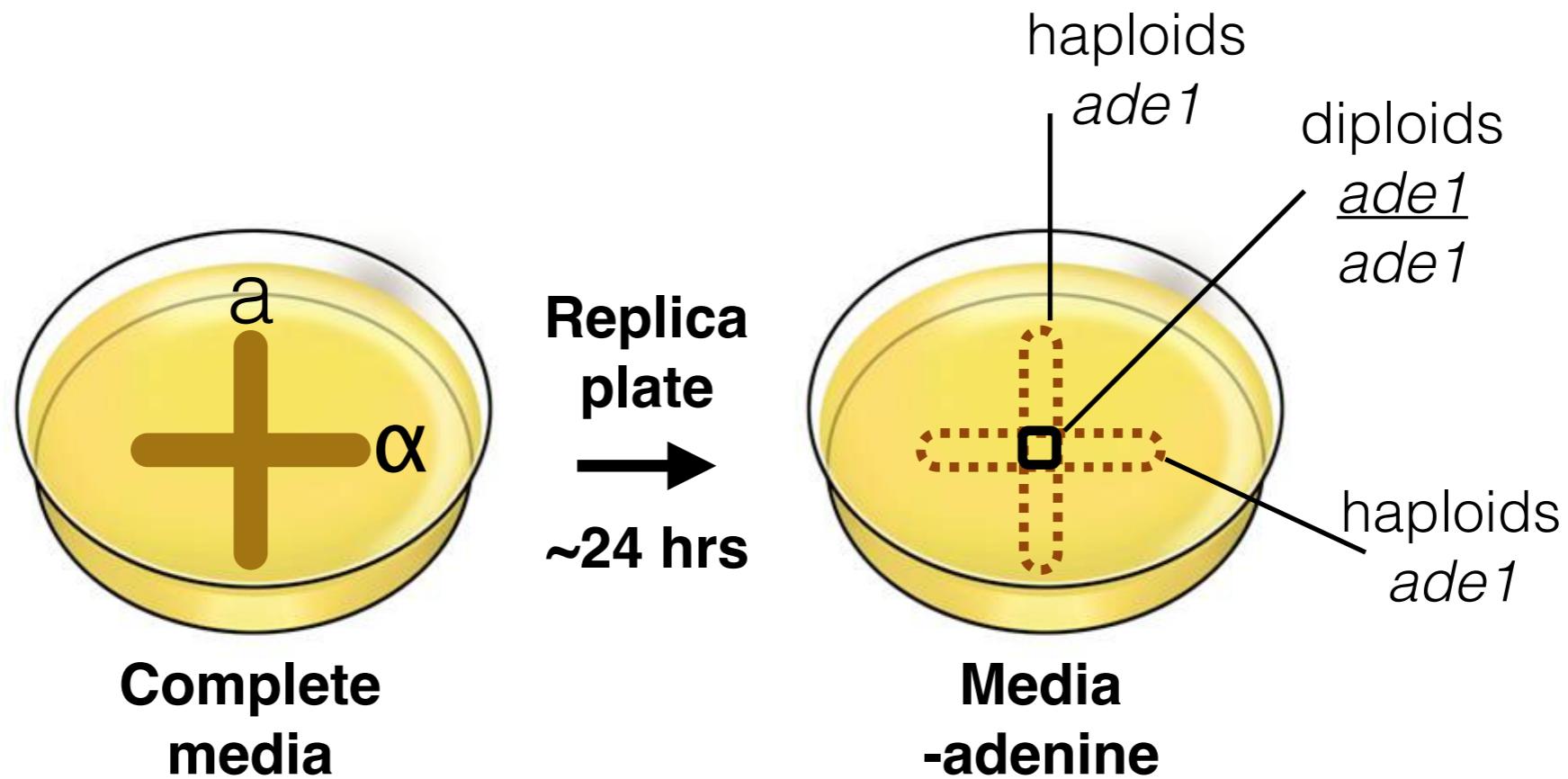
Yeast mating tests



ade1 mutant

a cells are *ade1* mutant
α cells are *ade1* mutant

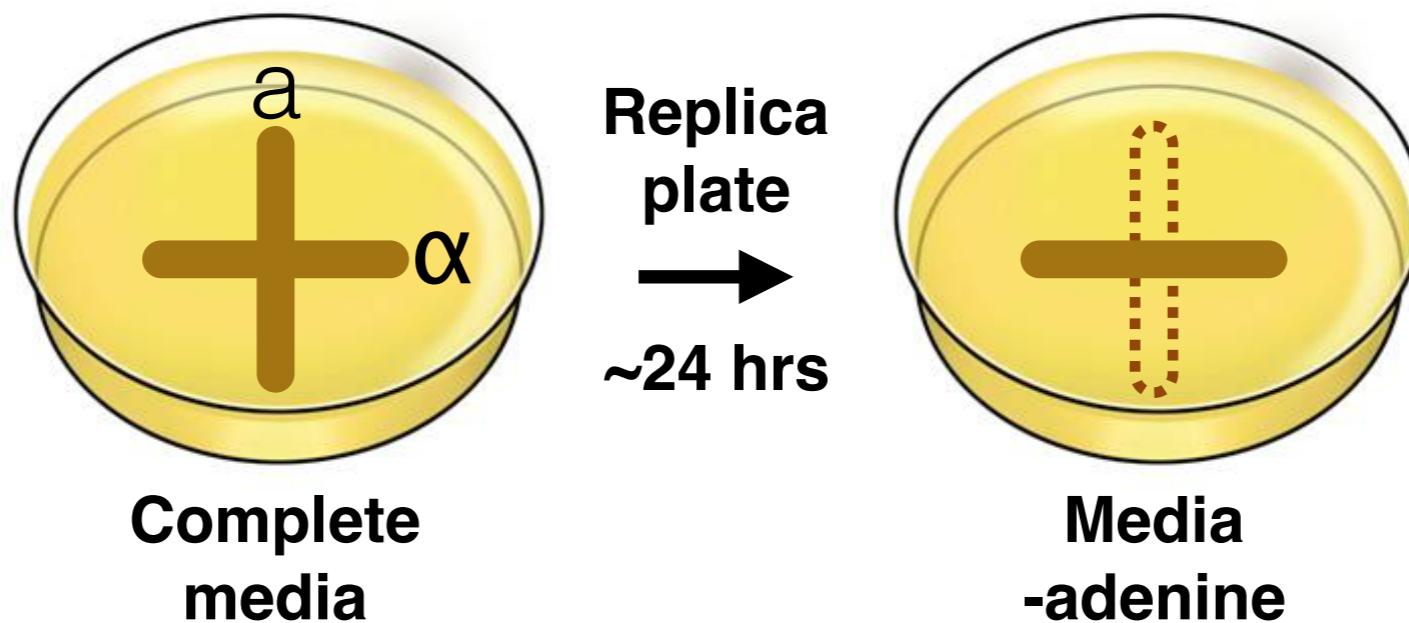
Yeast mating tests



a cells are *ade1* mutant

α cells are *ade1* mutant

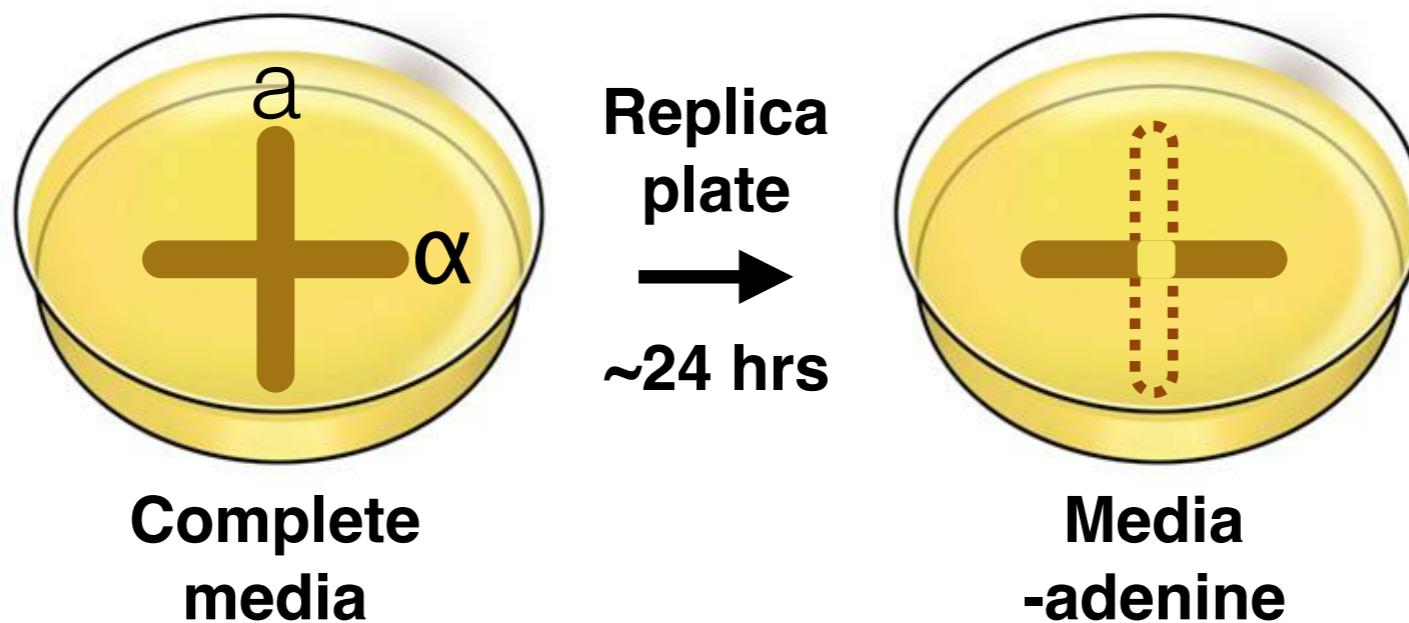
Dominance testing comes before complementation testing



a cells are *ade1* mutant
 α cells are wild-type

Is the mutant phenotype dominant?

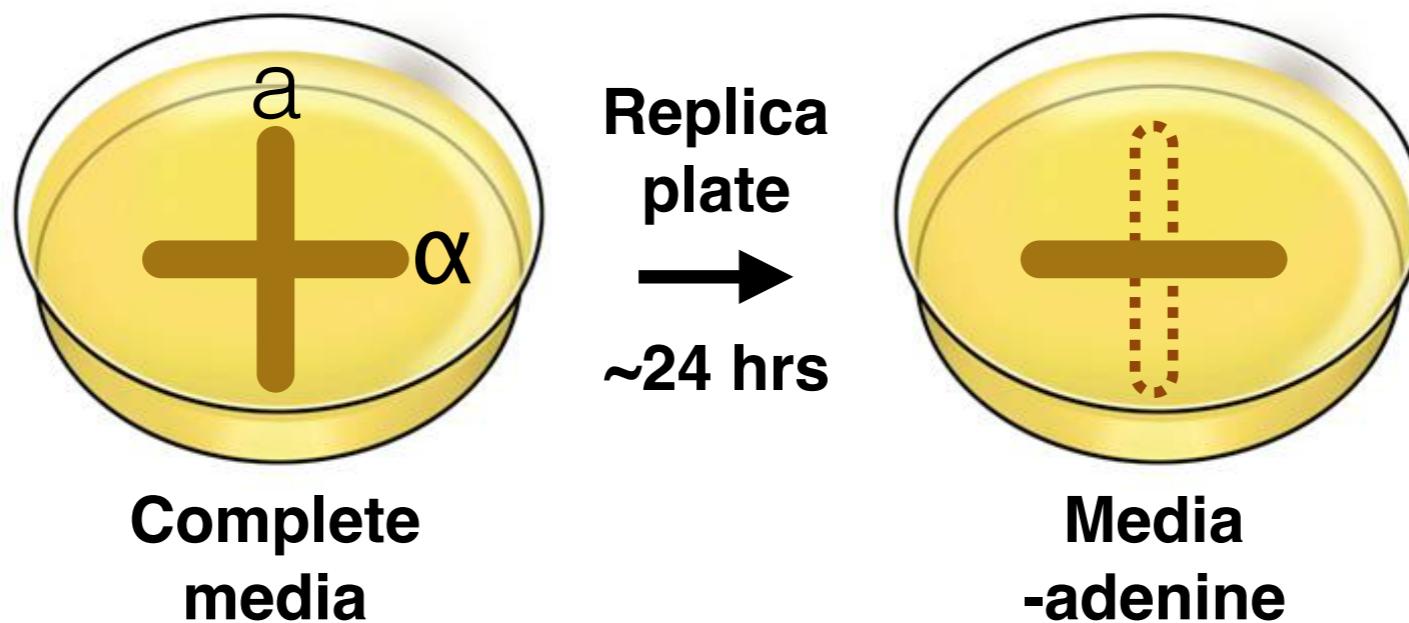
Dominance testing comes before complementation testing



a cells are *ade2* mutant
α cells are wild-type

Is the mutant phenotype dominant?

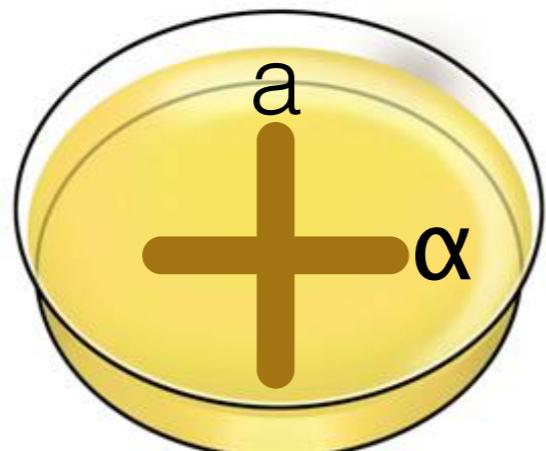
Dominance testing comes before complementation testing



a cells are *ade3* mutant
α cells are wild-type

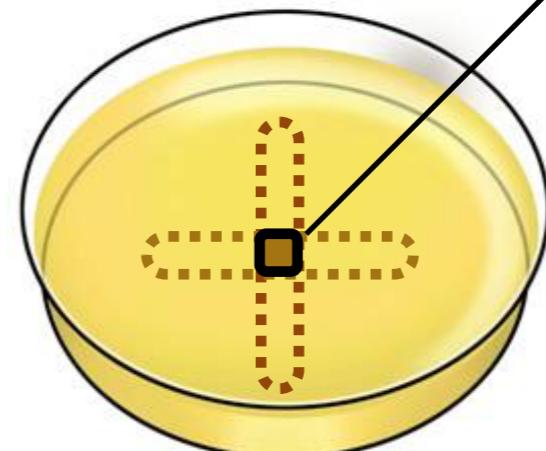
Is the mutant phenotype dominant?

The complementation test



Complete media

Replica plate
→
~24 hrs



Media -adenine

diploids
ade1 +
+ ade3

Gene	Phenotype
<i>ade1</i>	Rec.
<i>ade2</i>	Dom.
<i>ade3</i>	Rec.

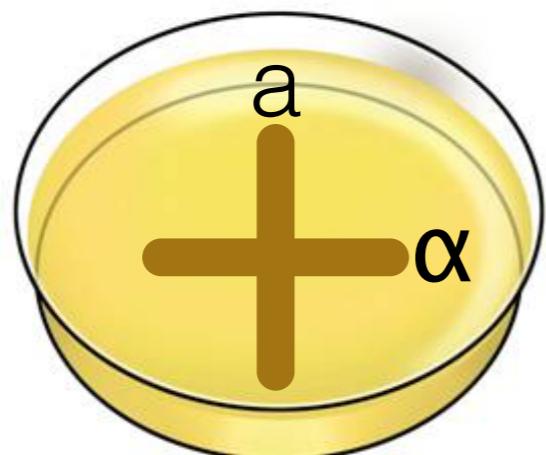
a cells are *ade1* mutant

α cells are *ade3* mutant

***ade1* and *ade3* mutations are in different genes**

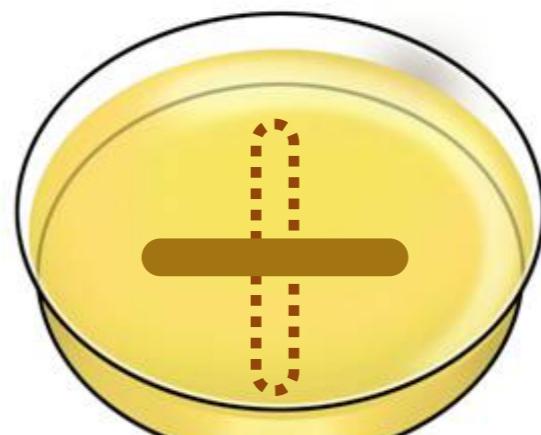
They are deficient in different functions!

Dominance testing comes before complementation testing



Complete media

Replica plate
→
~24 hrs



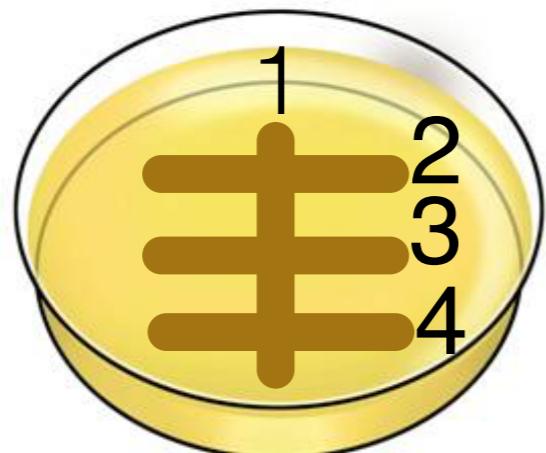
Media -adenine

a cells are *ade4* mutant
α cells are wild-type

Gene	Phenotype
<i>ade1</i>	Rec.
<i>ade2</i>	Dom.
<i>ade3</i>	Rec.

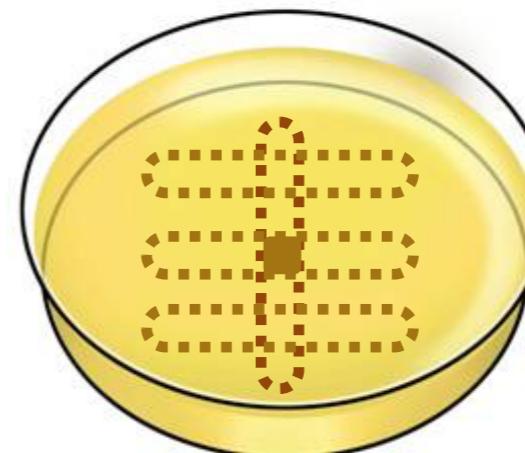
Is the mutant phenotype dominant?

The complementation test



Complete media

Replica plate
→
~24 hrs



Media -adenine

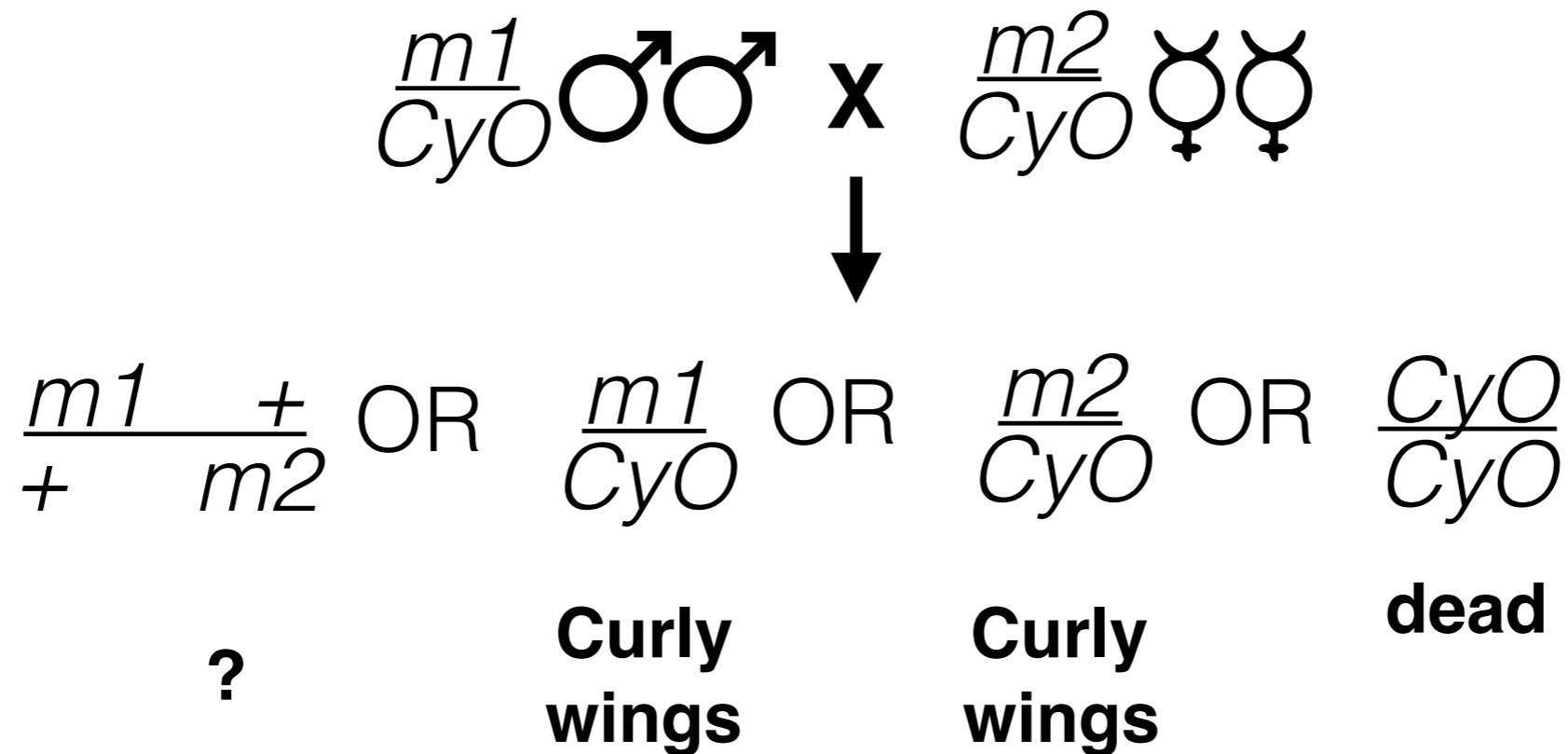
- a cells are *ade1* mutant
- α cells are *ade2* mutant
- α cells are *ade3* mutant
- α cells are *ade4* mutant

Gene	Phenotype
<i>ade1</i>	Rec.
<i>ade2</i>	Dom.
<i>ade3</i>	Rec.
<i>ade4</i>	Rec.

***ade1* and *ade4* mutations are in the same gene**

They are deficient in the same function

The complementation test - *Drosophila*



It is easy to control crosses using obligate outcrossers (e.g. males and females)

The complementation test - *C. elegans*



$\frac{m1}{m1}$ ♂ x $\frac{m2}{m2}$ ♀



$\frac{m1}{+}$ +
+ $m2$

The complementation test - *C. elegans*



$\frac{m1}{m1}$ ♂ x $\frac{m2}{m2}$ ♀
↓ ↓

$\frac{m1}{+}$ $\frac{m2}{m2}$

The complementation test - *C. elegans*



$\frac{m1}{m1}$ ♂ x $\frac{dpy-5}{dpy-5}$; $\frac{m2}{m2}$ ♀



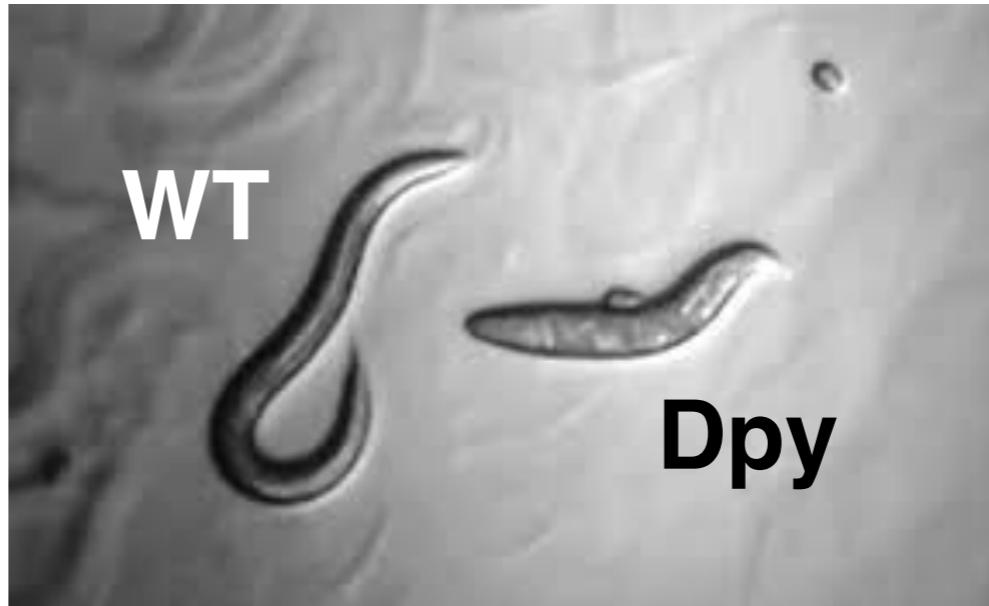
The complementation test - *C. elegans*



$\frac{m1}{m1}$ ♂ x $\frac{dpy-5}{dpy-5}$; $\frac{m2}{m2}$ ♀



$\frac{dpy-5}{+}$; $\frac{m1}{+}$ + $\frac{m2}{m2}$ $\frac{dpy-5}{dpy-5}$; $\frac{m2}{m2}$

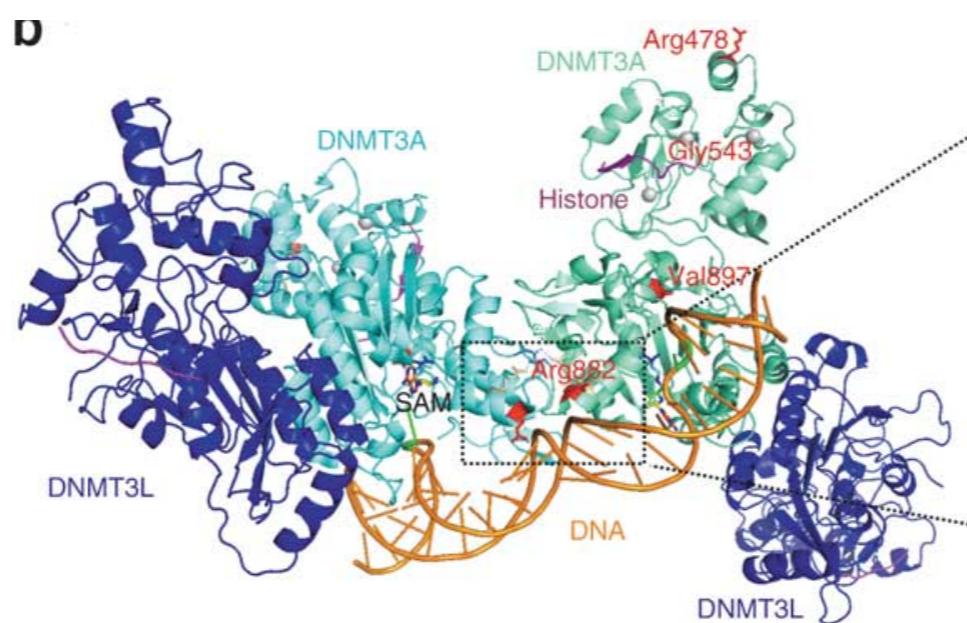


Why do we care about complementation?

- Multiple alleles of a gene allow us to probe gene function



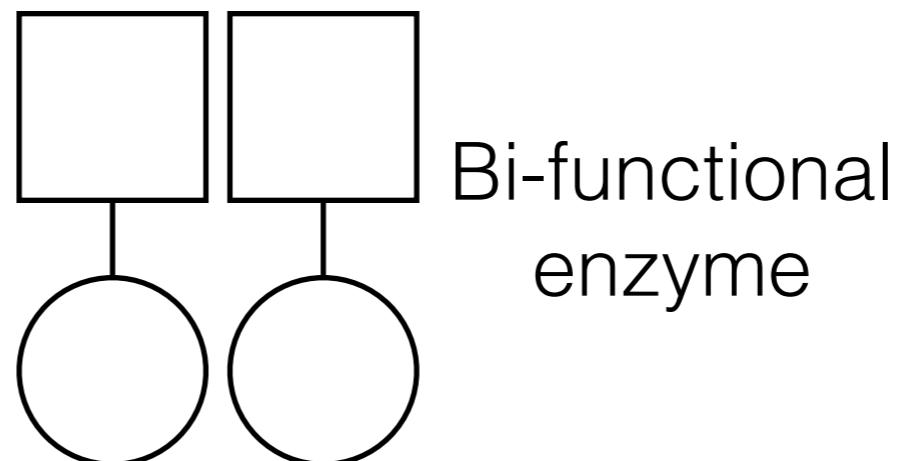
- Different alleles affect different parts of gene



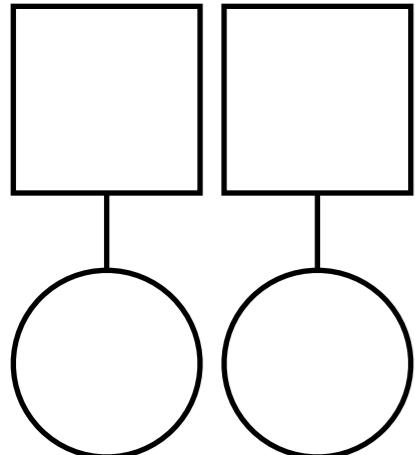
Exceptions to complementation of function

Intragenic complementation

same gene but different functions

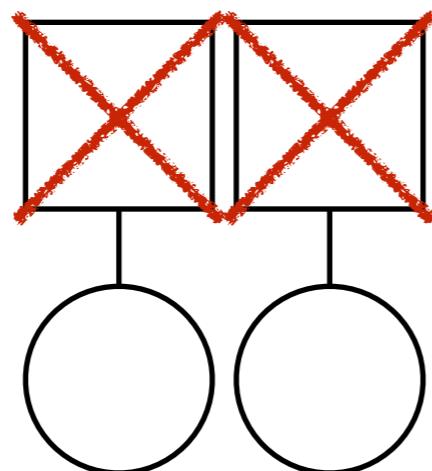


Wild-type



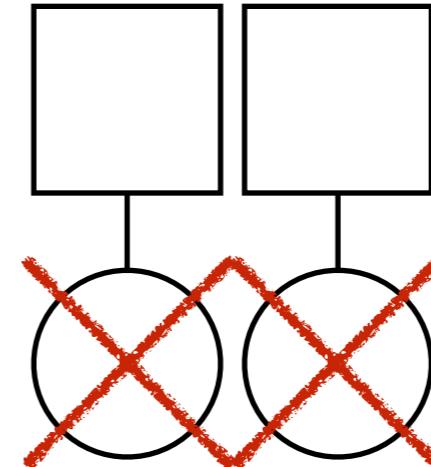
±
+

Mutant



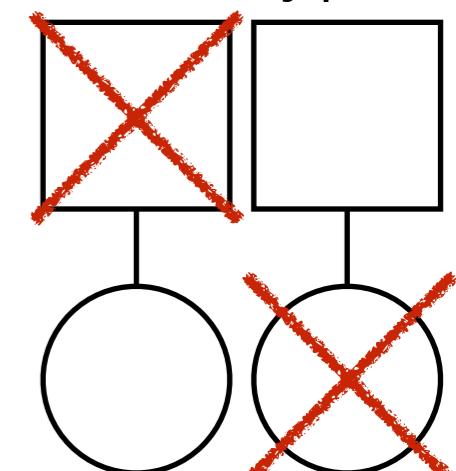
mutation1
mutation1

Mutant



mutation2
mutation2

Wild-type

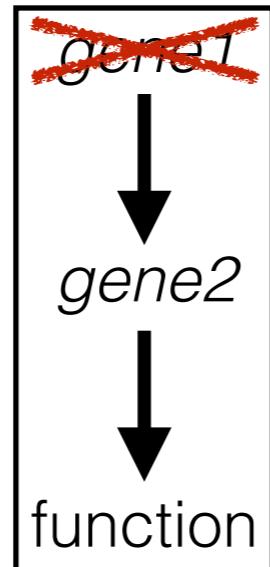
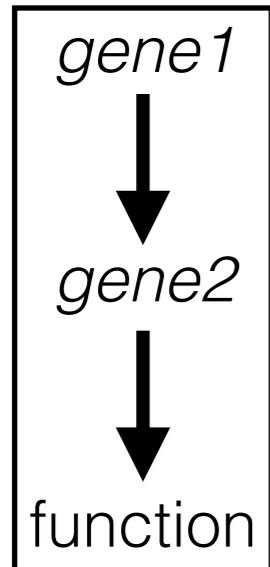
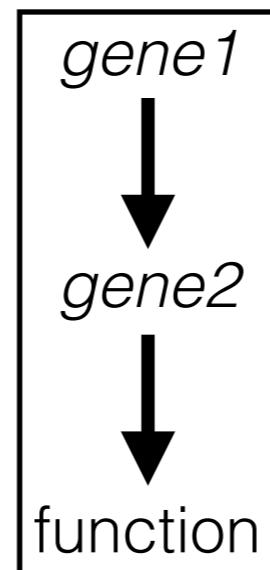


mutation1
mutation2

Exceptions to complementation of function

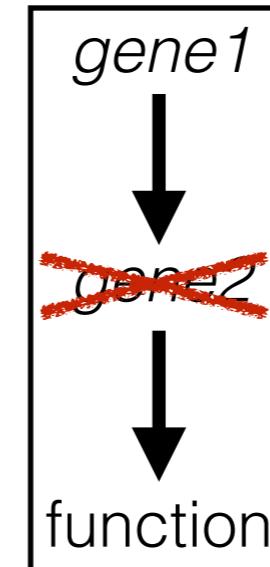
Intergenic noncomplementation

different gene but same function

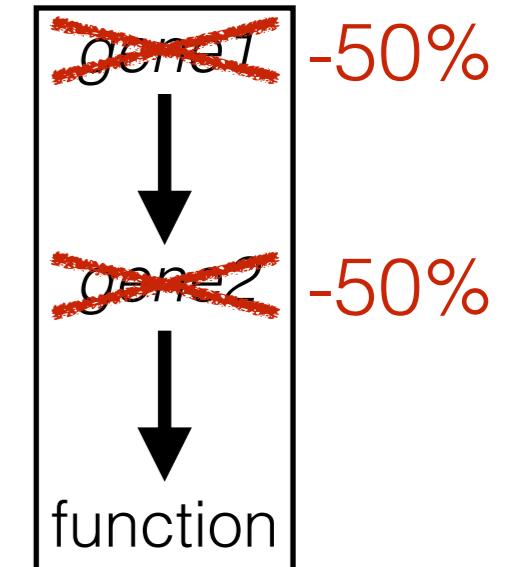


±
+

mut. g1
mut. g1



mut. g2
mut. g2

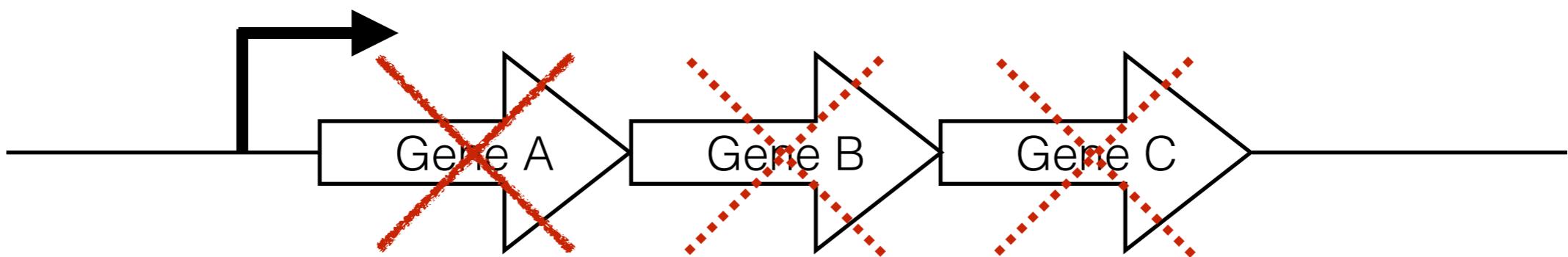
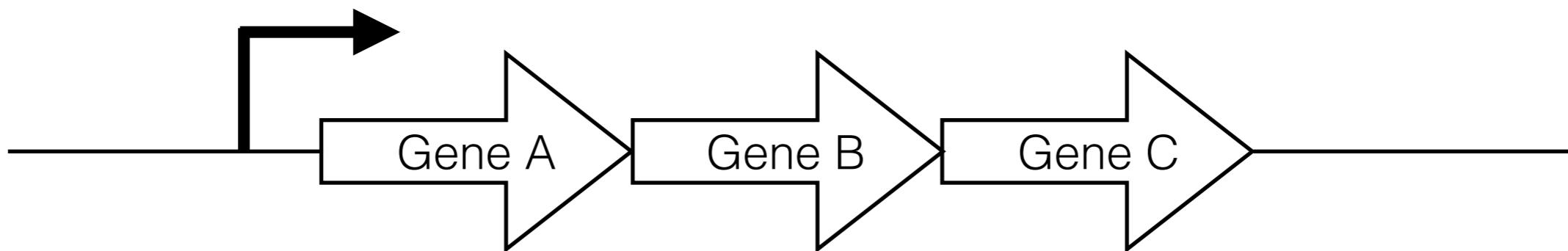


mut. g1 +
+ mut. g2

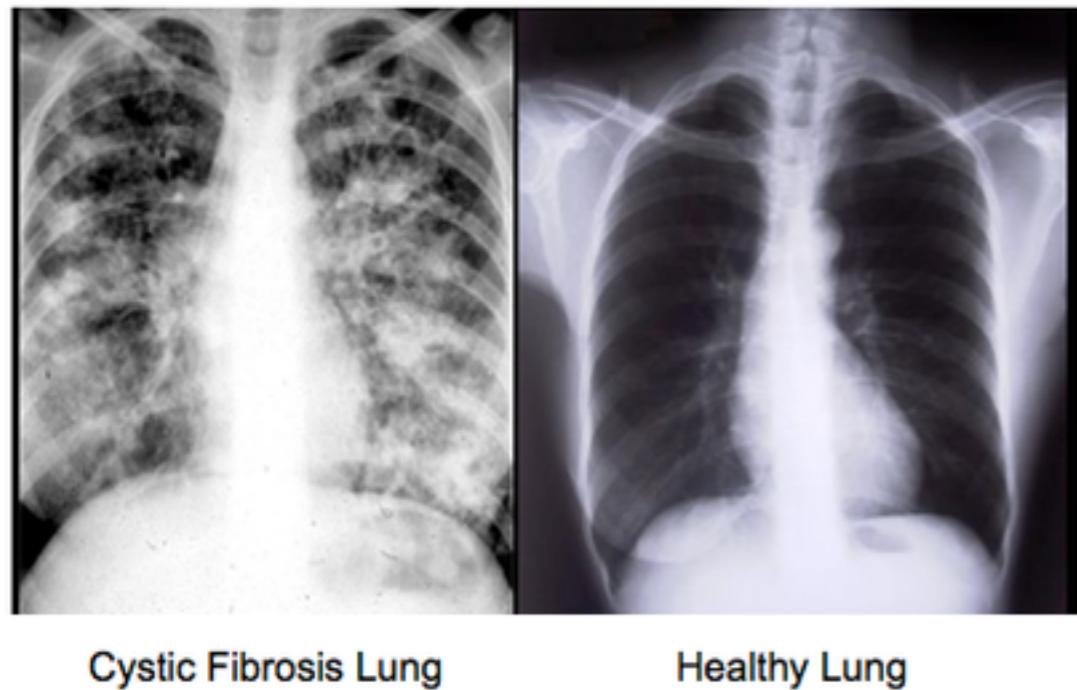
Exceptions to complementation of function

Polar effects

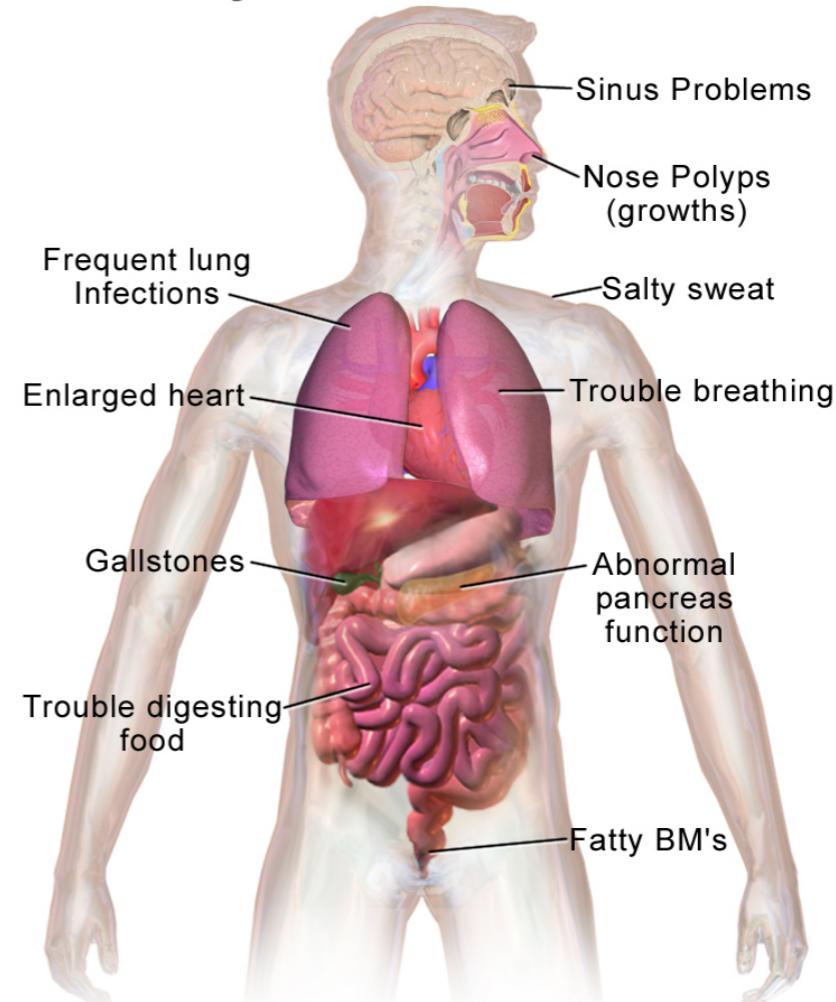
one mutation affects multiple genes/functions



What about cystic fibrosis and today's topic?

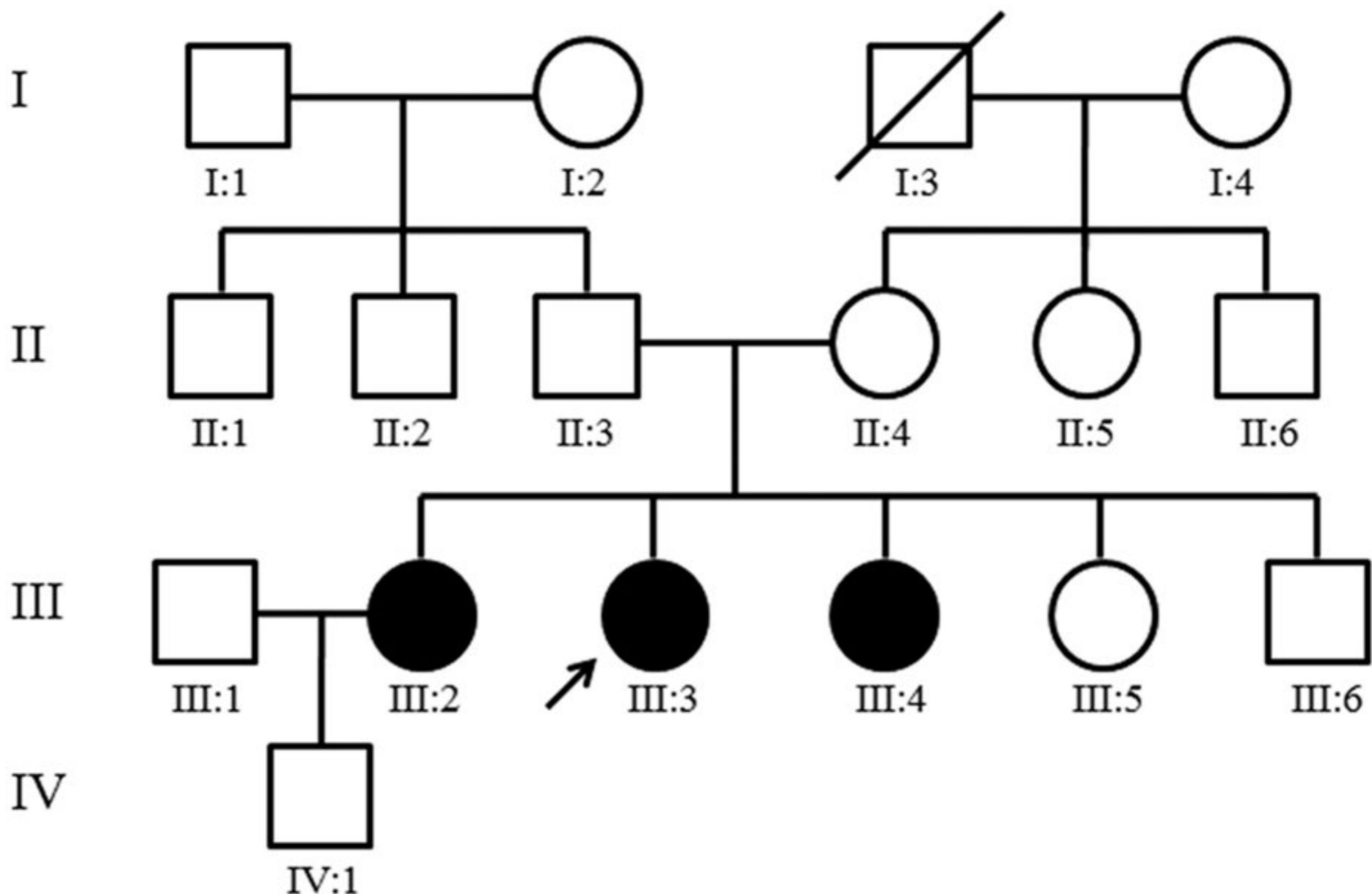


Health Problems with Cystic Fibrosis

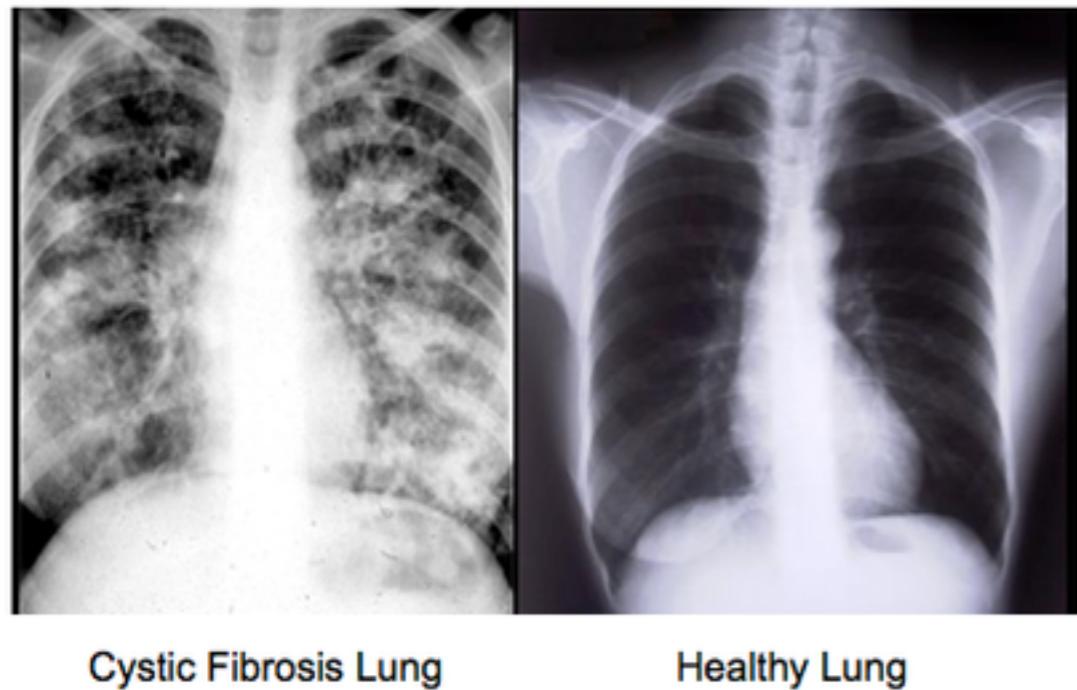


1. Autosomal recessive disorder
2. Not caused by chromosomal aberrations or meiotic NDJ
3. Mapped to chromosome 7
4. Mutants in CF gene are null or hypomorphs

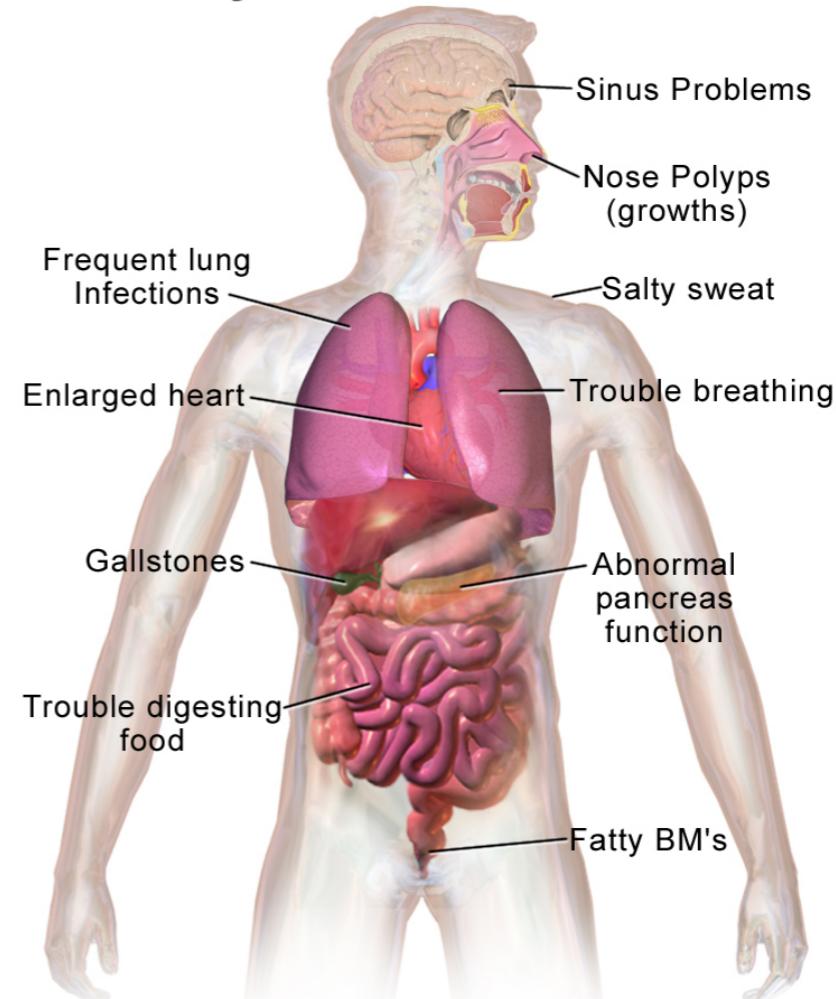
Compound heterozygosity - failure to complement



What about cystic fibrosis and today's topic?



Health Problems with Cystic Fibrosis



1. Autosomal recessive disorder
2. Not caused by chromosomal aberrations or meiotic NDJ
3. Mapped to chromosome 7
4. Mutants in CF gene are null or hypomorphs
5. Mutants can be compound heterozygotes between two different mutations