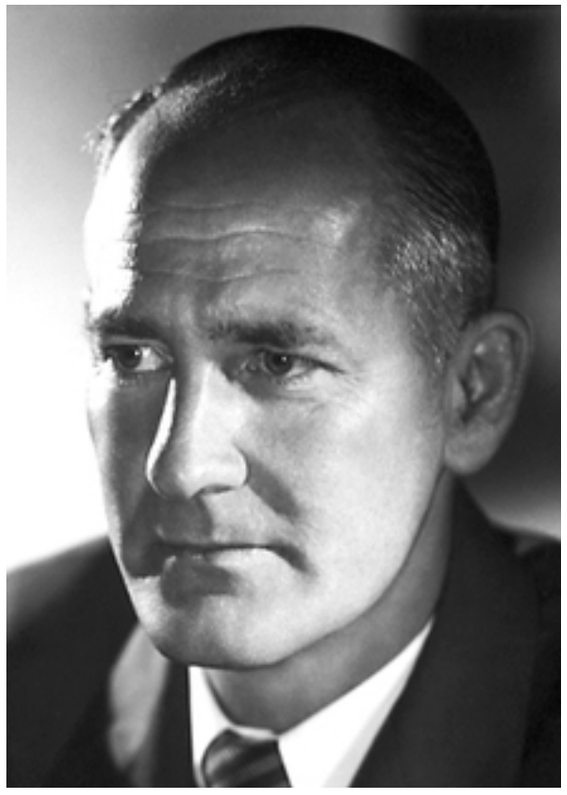
Bio393: Genetic Analysis

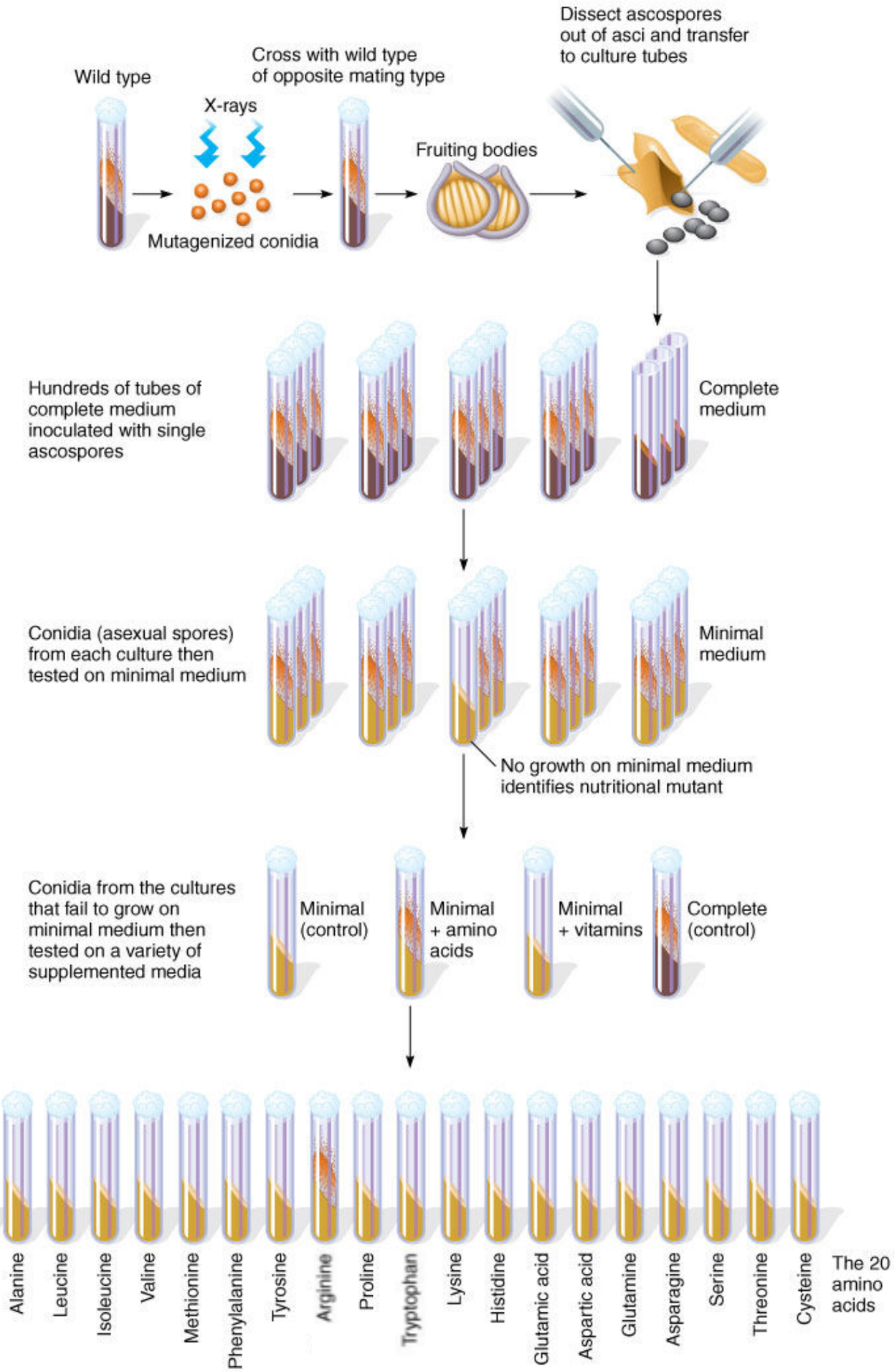
Genetic interactions: epistasis



George Beadle

Ed Tatum

The Beadle-Tatum Experiment



Arginine mutant complementation experiment

	arg-a	*arg-b*	*arg-c*	*arg-d*	*arg-e*	*arg-f*	*arg-g*	*arg-h*	*arg-i*
arg-a		■	■		■			■	■
arg-b	■			■	■	■	■	■	■
arg-c	■			■	■	■	■	■	■
arg-d		■	■		■			■	■
arg-e	■	■	■	■		■	■		
arg-f		■	■		■			■	■
arg-g		■	■		■			■	■
arg-h	■	■	■	■		■	■		
arg-i	■	■	■	■		■	■		

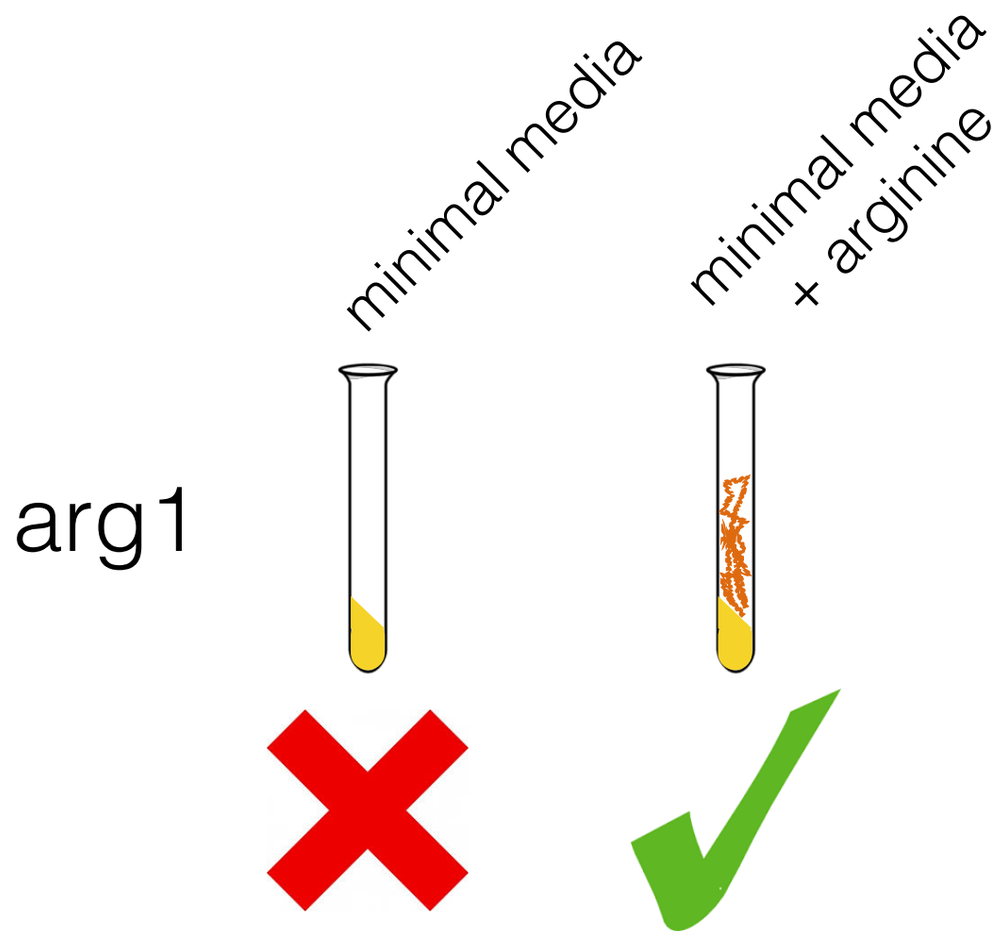
Arginine mutant complementation experiment

Three genes

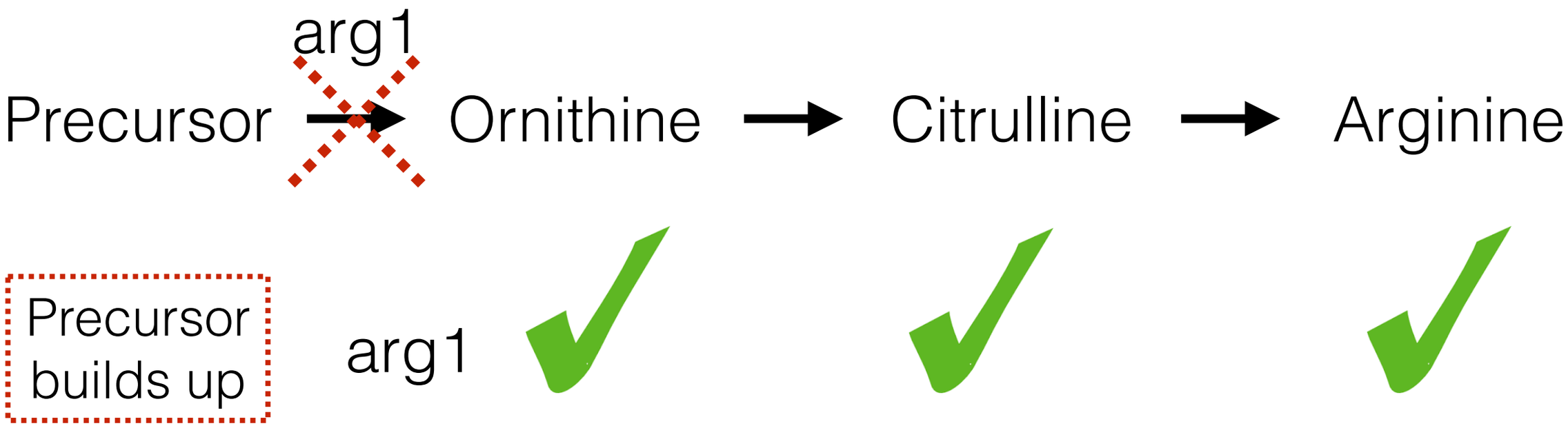
arg1 = [a, d, f, g]

arg2 = [b, c]

arg3 = [e, h, i]

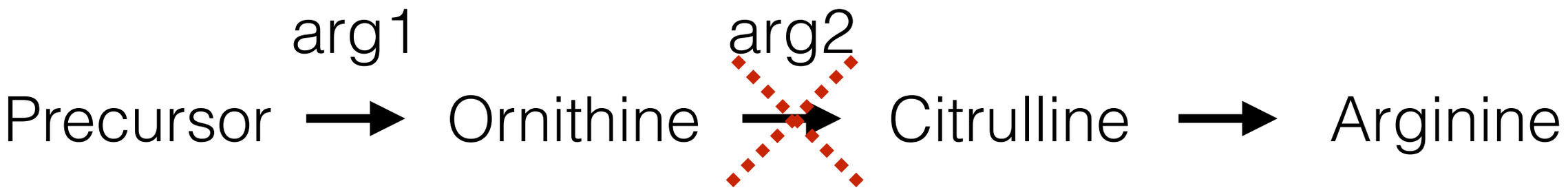


One gene - one enzyme hypothesis



Mutants accumulate precursor for previous step

One gene - one enzyme hypothesis



Precursor builds up

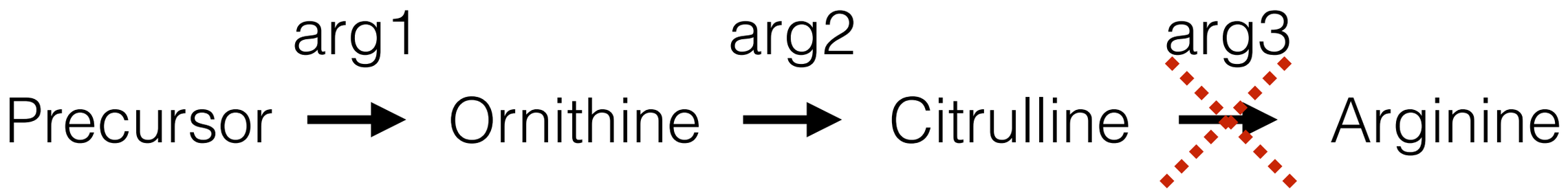
arg1 ✓ ✓ ✓

Ornithine builds up

arg2 ✗ ✓ ✓

Mutants accumulate precursor for previous step

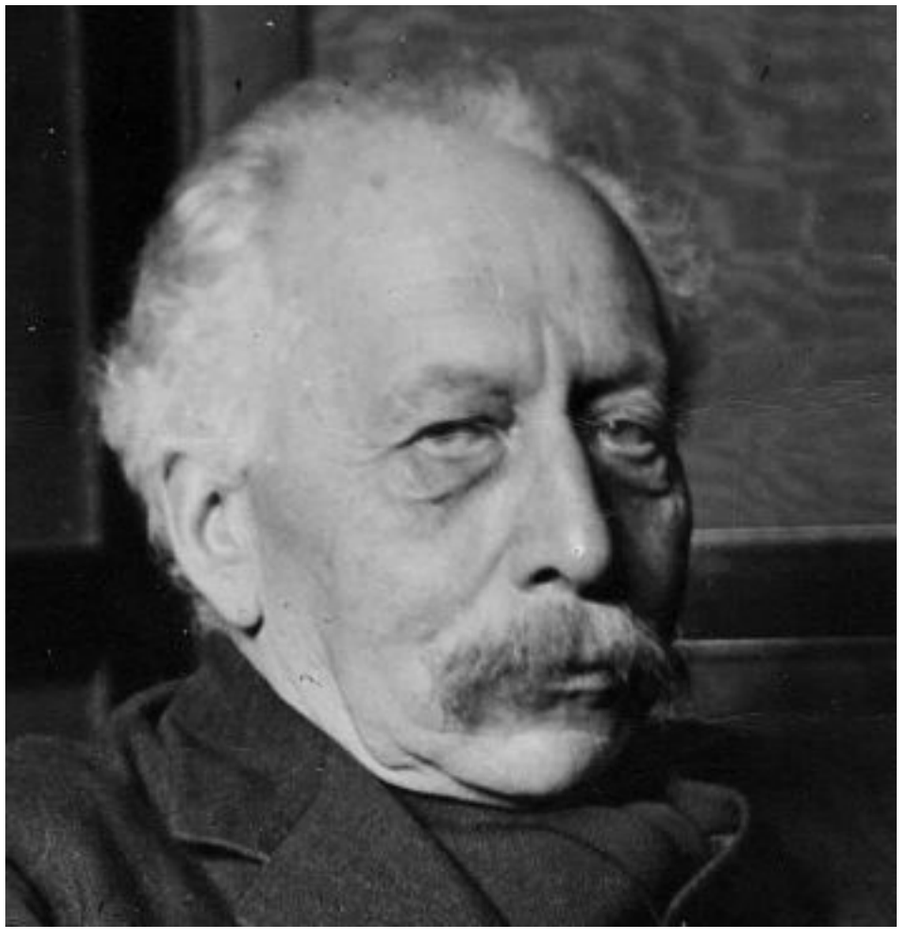
One gene - one enzyme hypothesis



Precursor builds up	arg1	✓	✓	✓
Ornithine builds up	arg2	✗	✓	✓
Citrulline builds up	arg3	✗	✗	✓

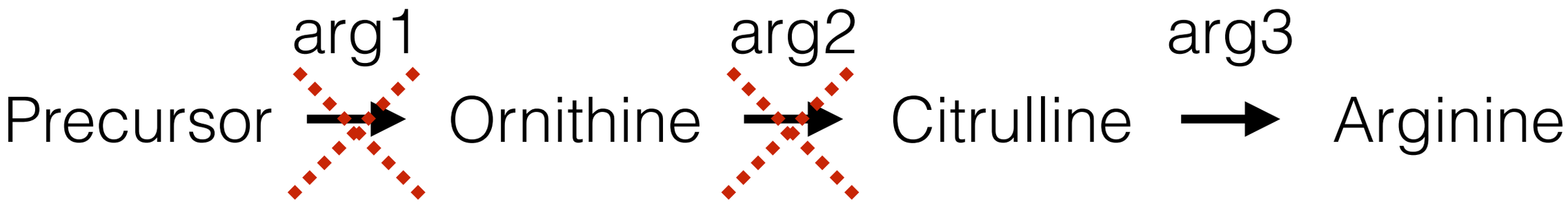
Mutants accumulate precursor for previous step

Epistasis
the effect of one gene is dependent on another gene



William Bateson

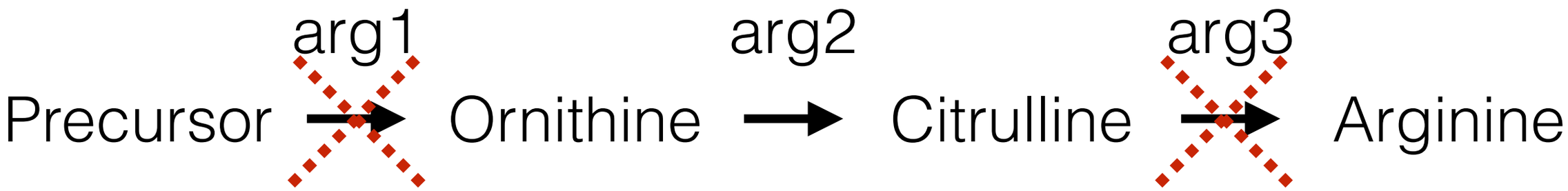
Biochemical epistasis



arg1	✓	✓	✓
arg2	✗	✓	✓
arg3	✗	✗	✓
Precursor builds up **arg2 = arg1 arg2**	✗	✓	✓

arg2 is epistatic to arg1, arg2 is downstream (or in parallel) to arg1 **Lecture 6**

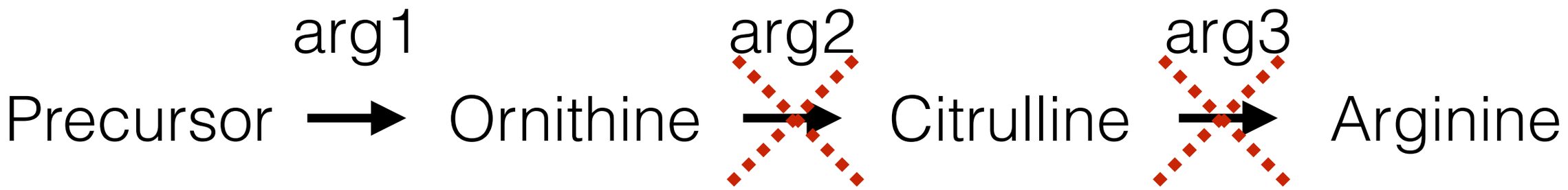
Biochemical epistasis



arg1	✓	✓	✓
arg2	✗	✓	✓
arg3	✗	✗	✓
Precursor builds up **arg2 = arg1 arg2**	✗	✓	✓
Precursor builds up **arg3 = arg1 arg3**	✗	✗	✓

arg3 is epistatic to arg1, arg3 is downstream (or in parallel) to arg1 **Lecture 6**

Biochemical epistasis



	Precursor	Ornithine	Citrulline	Arginine
arg1		✓	✓	✓
arg2		✗	✓	✓
arg3		✗	✗	✓
Precursor builds up	**arg2 = arg1 arg2**	✗	✓	✓
Precursor builds up	**arg3 = arg1 arg3**	✗	✗	✓
Ornithine builds up	**arg3 = arg2 arg3**	✗	✗	✓

arg3 is epistatic to arg2, arg3 is downstream (or in parallel) to arg1

Approach to understanding biochemical epistasis

1. Single mutants fail in a step in a biosynthetic pathway

2. Double mutants fail in two steps. The growth phenotype dictates the most downstream gene in the pathway. The compound built up dictates the most upstream gene in the pathway.

3. What will the single and double mutants accumulate?

4. Pathways can be branched

Epistasis - one mutant phenotype trumps another

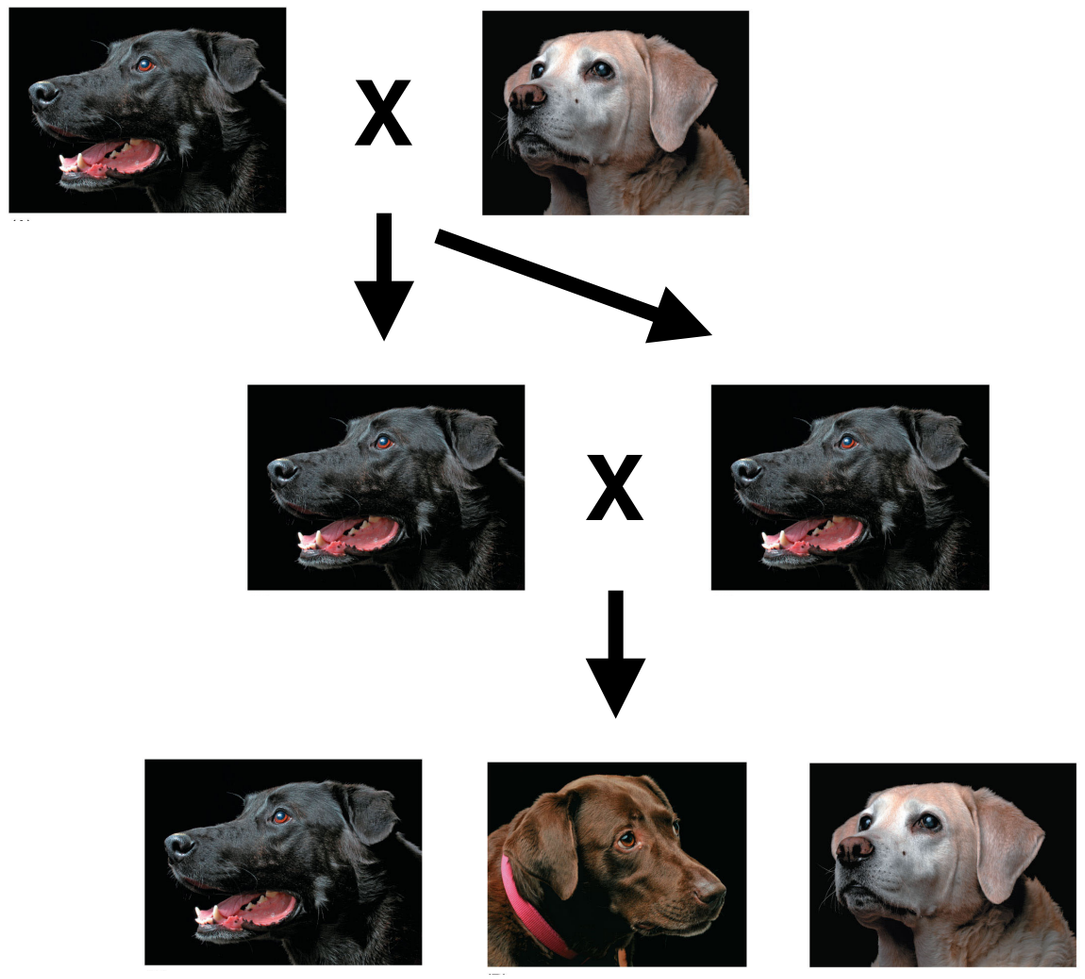
(A)

(B)

(C)

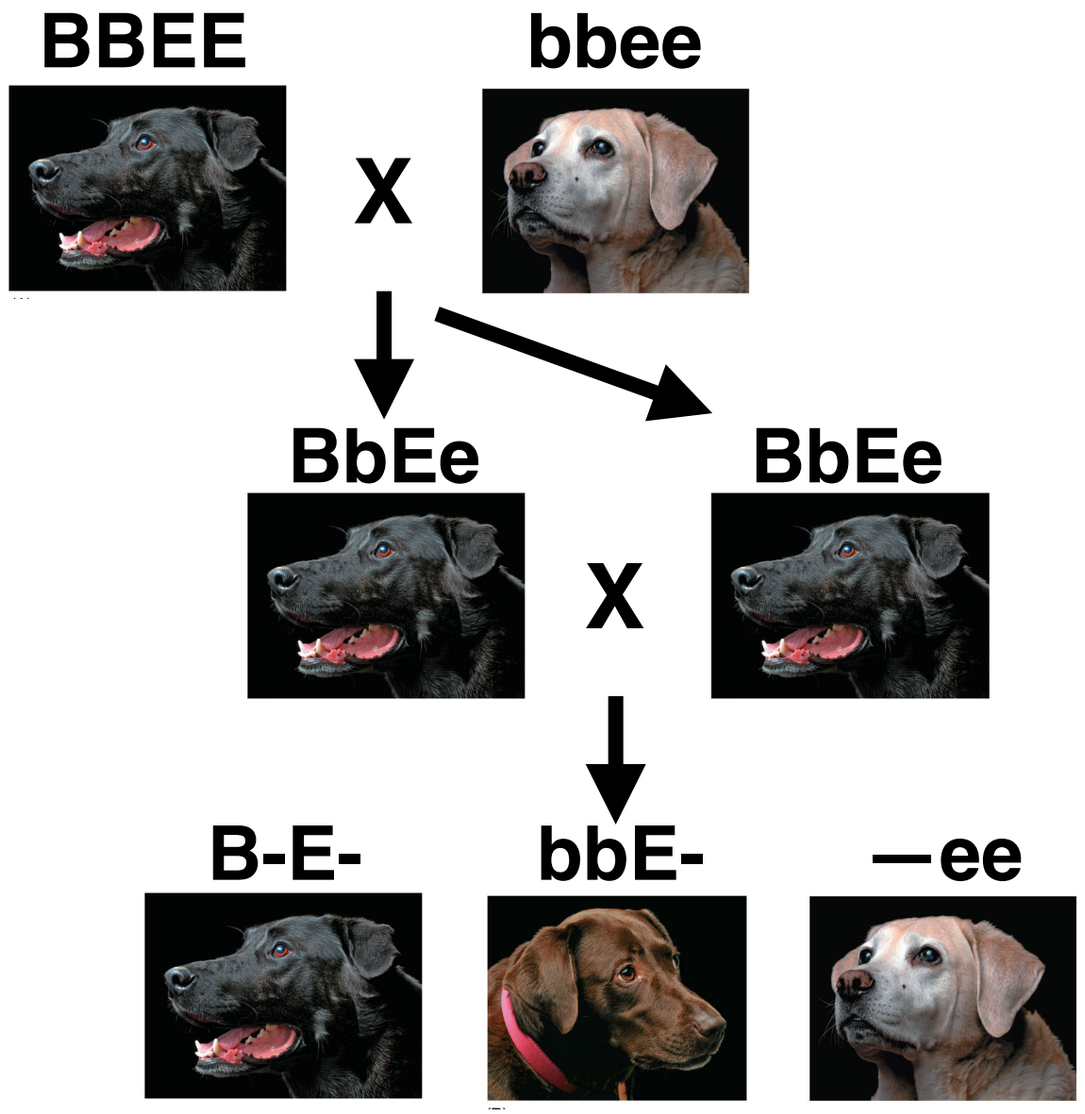
***LIFE 8e*, Figure 10.14**

Epistasis - one mutant phenotype trumps another



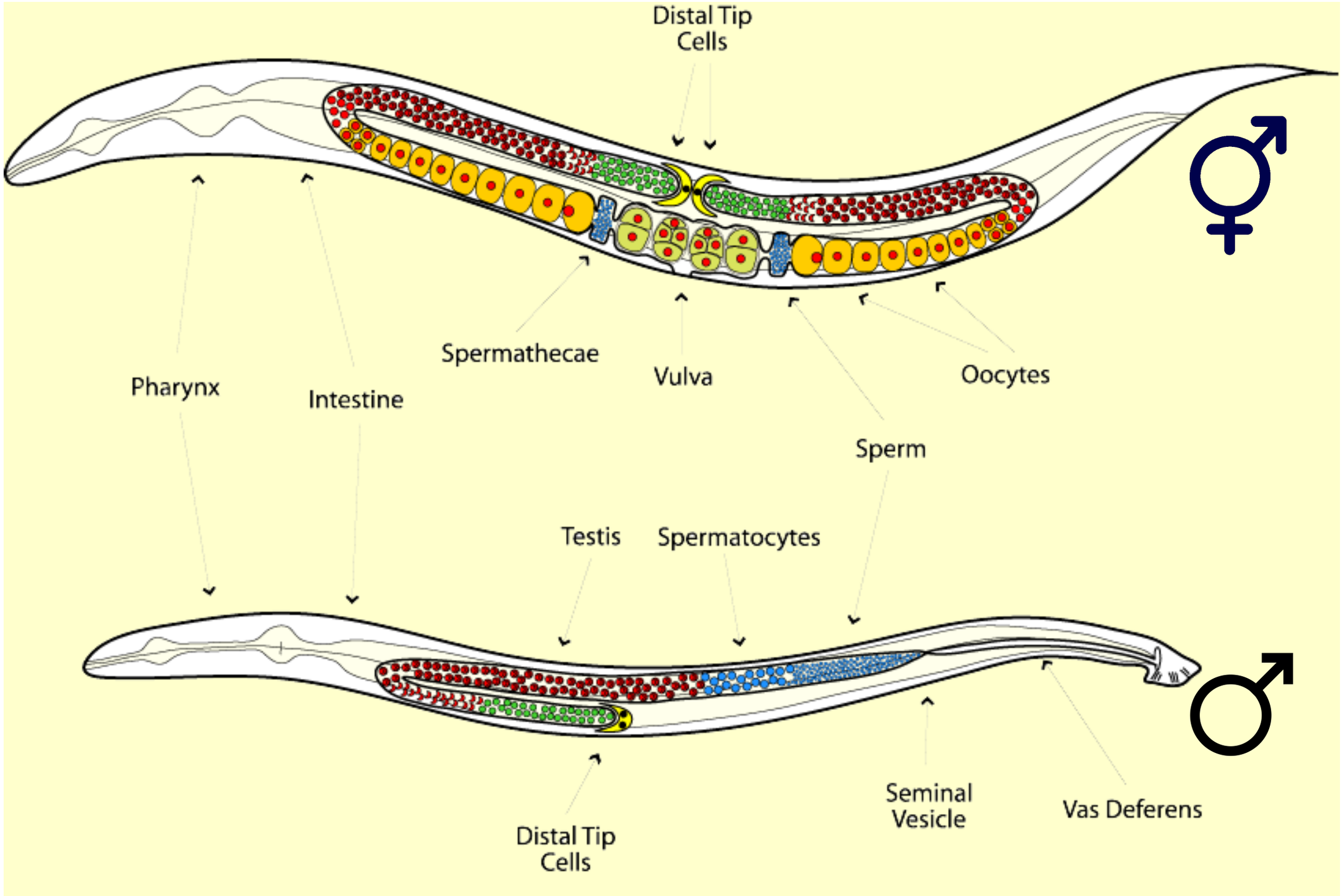
9 : 3 : 4

Epistasis - one mutant phenotype trumps another

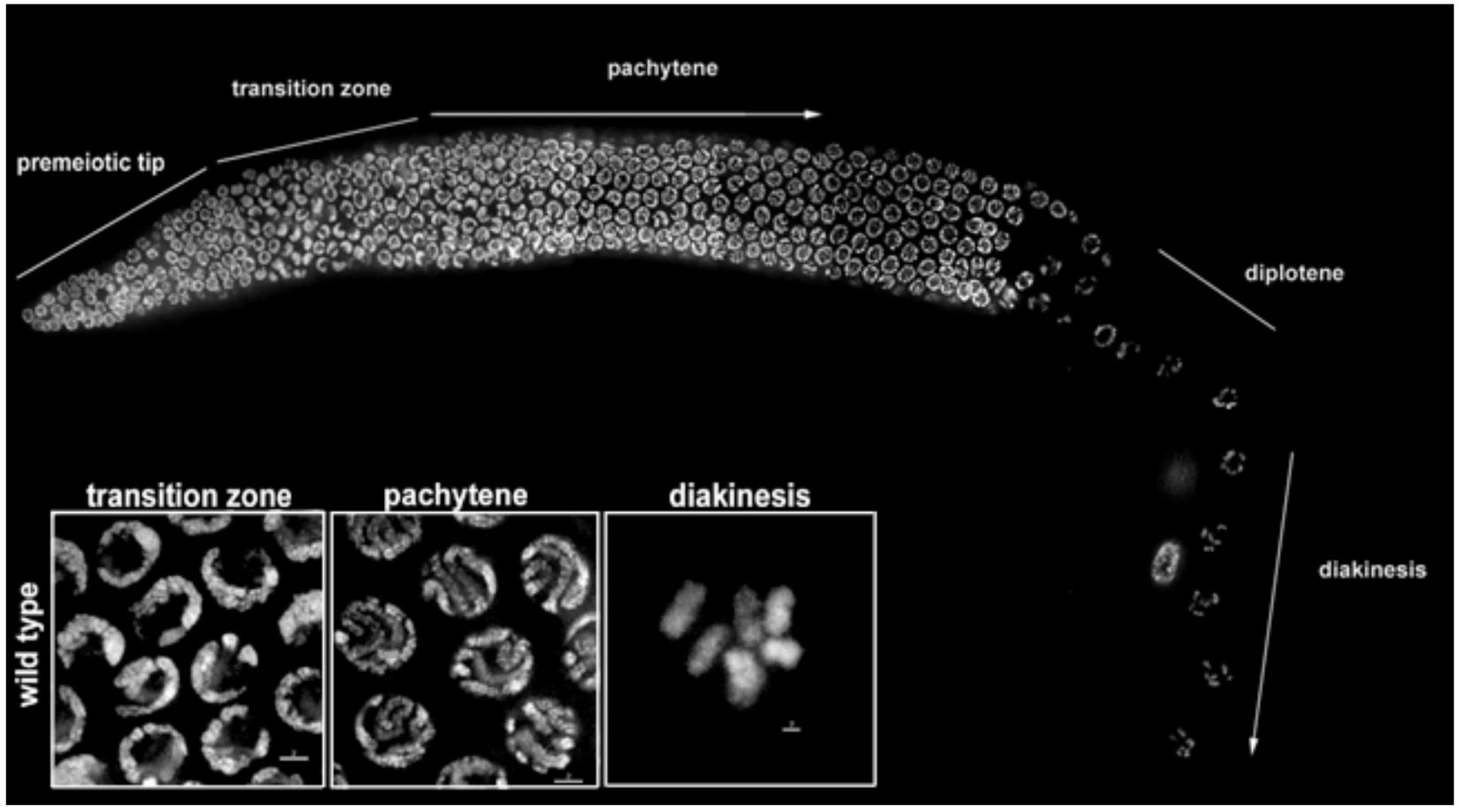


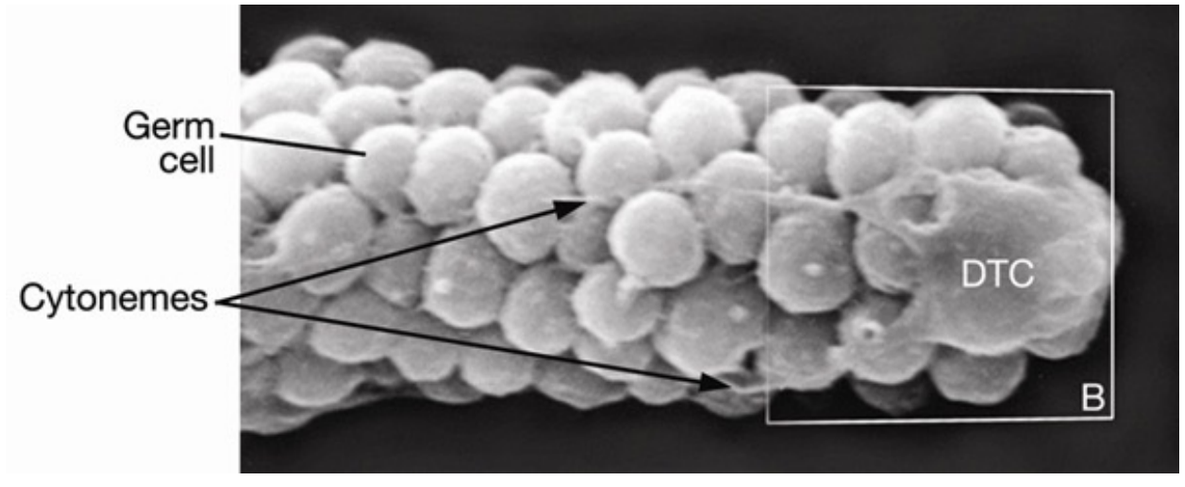
B = black
b = brown
E = color
e = no color

The *C. elegans* germline



The *C. elegans* germline

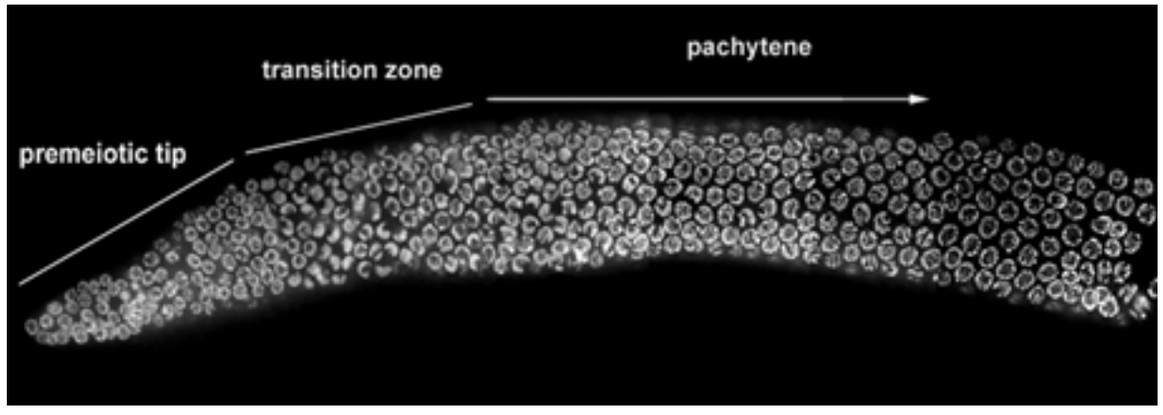


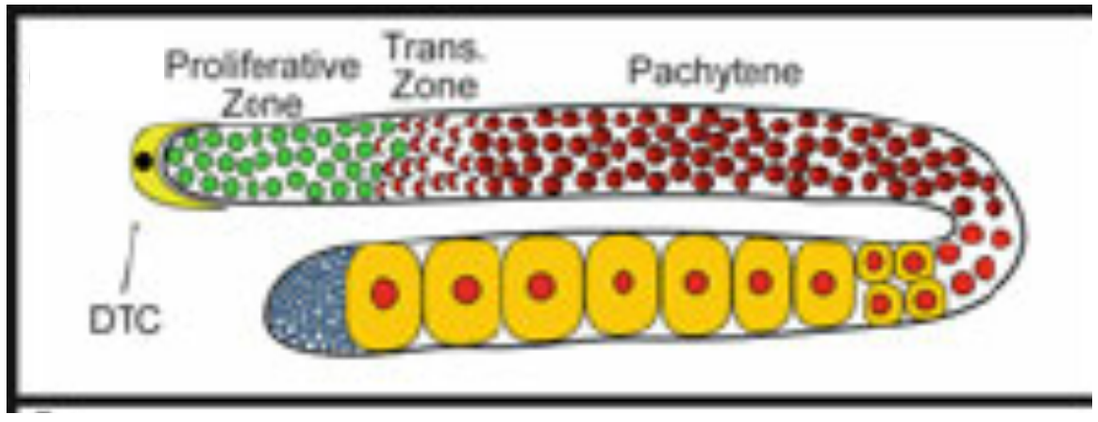


Judith Kimble

Lecture 6

C. elegans germline mutants



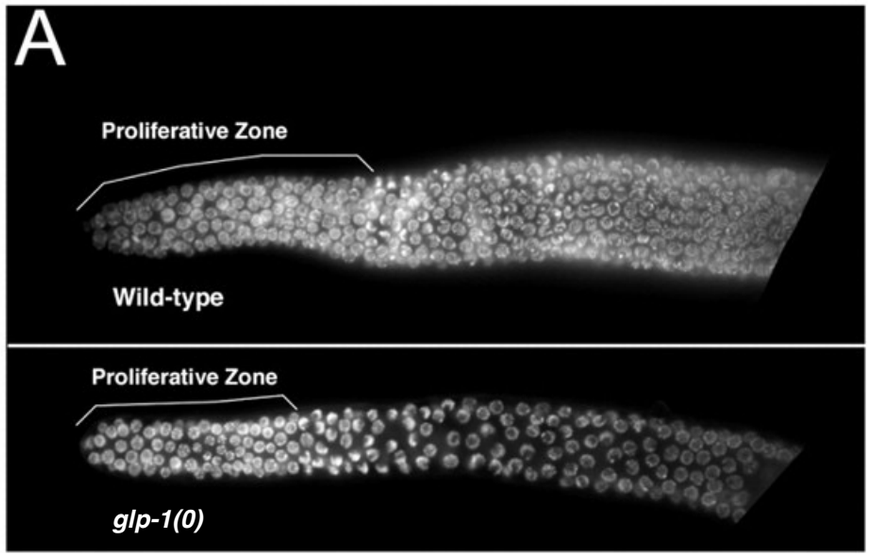


glp-1(0) = all meiotic germ cells

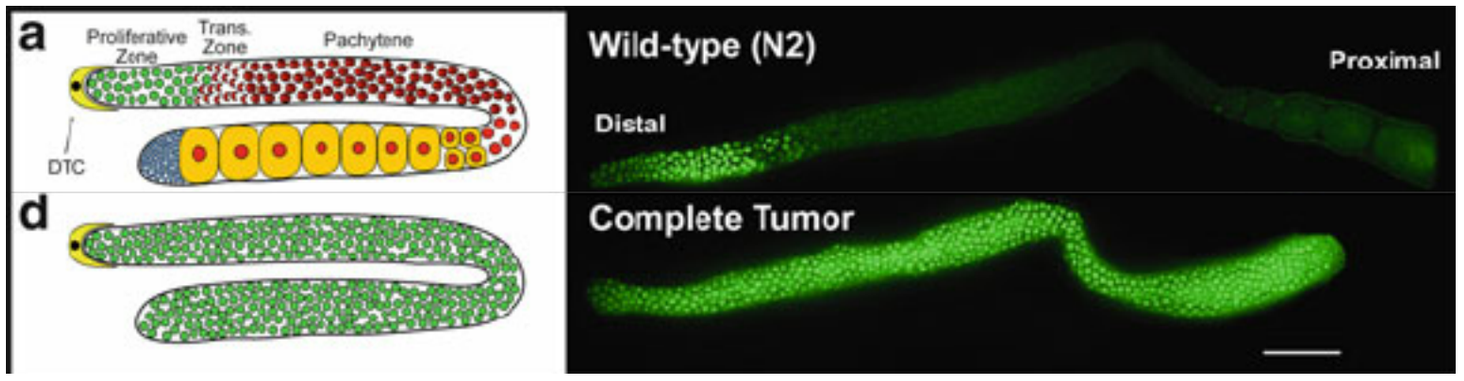
glp-1(gf) = all mitotic germ cells

glp-1 → **germ cell proliferation**

C. elegans germline mutants



glp-1(0) =
more meiosis, less mitosis



glp-1(gf) =
more mitosis,
less meiosis

glp-1 ⟶ **germ cell proliferation**

C. elegans germline mutants

Mutant	Phenotype	
glp-1(0)	meiotic cells	***glp-1*** → **GSC prolif.**
glp-1(gf)	mitotic cells	
lag-2(0)	meiotic cells	***lag-2*** → **GSC prolif.**
fbf-1(0)	meiotic cells	***fbf-1*** → **GSC prolif.**
gld-1(0)	mitotic cells	***gld-1*** ⊣ **GSC prolif.**

How do these genes work together?

Mutant	Phenotype
glp-1(0)	meiotic cells
glp-1(gf)	mitotic cells
lag-2(0)	meiotic cells
fbf-1(0)	meiotic cells
gld-1(0)	mitotic cells
glp-1(0); lag-2(0)	meiotic cells

You can only do epistasis tests with mutants that have different phenotypes

How do these genes work together?

Mutant	Phenotype
glp-1(0)	meiotic cells
glp-1(gf)	mitotic cells
lag-2(0)	meiotic cells
fbf-1(0)	meiotic cells
gld-1(0)	mitotic cells
glp-1(gf); lag-2(0)	mitotic cells

glp-1 → **GSC prolif.**

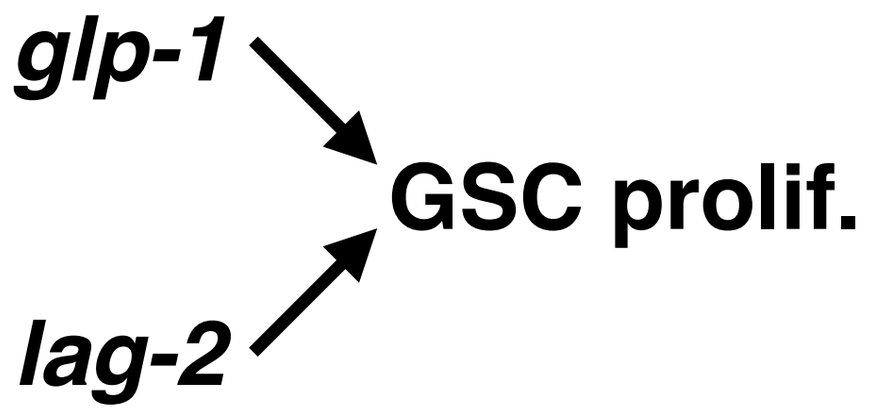
lag-2 → **GSC prolif.**

Which phenotype is epistatic?

lag-2 → ***glp-1*** → **GSC prolif.**

Parallel gene action can NEVER be formally excluded by phenotype alone

lag-2 → ***glp-1*** → **GSC prolif.**



Null alleles have to be used for this reason.

Approach to understanding regulatory epistasis

1. Decide what is the output phenotype; keep it consistent

2. Look at single mutants and make a model with output

3. Look at double mutants and make a model with output and respect to single mutant models - epistatic gene acts downstream

4. Remember parallel but don't assume it is always parallel (*i.e.* make linear models for regulatory epistasis)

5. Remember two negatives make a positive

How do these genes work together?

Mutant	Phenotype
glp-1(0)	meiotic cells
glp-1(gf)	mitotic cells
lag-2(0)	meiotic cells
fbf-1(0)	meiotic cells
gld-1(0)	mitotic cells
glp-1(gf); lag-2(0)	mitotic cells
glp-1(gf); fbf-1(0)	meiotic cells
glp-1(0); gld-1(0)	mitotic cells
fbf-1(0); gld-1(0)	mitotic cells
lag-2(0); fbf-1(0)	meiotic cells
lag-2(0); gld-1(0)	mitotic cells

glp-1 → **GSC prolif.**

lag-2 → **GSC prolif.**

fbf-1 → **GSC prolif.**

gld-1 ⊣ **GSC prolif.**

lag-2 → ***glp-1*** → **GSC prolif.**

How do these genes work together?

Mutant	Phenotype
glp-1(0)	meiotic cells
glp-1(gf)	mitotic cells
lag-2(0)	meiotic cells
fbf-1(0)	meiotic cells
gld-1(0)	mitotic cells
glp-1(gf); lag-2(0)	mitotic cells
glp-1(gf); fbf-1(0)	meiotic cells
glp-1(0); gld-1(0)	mitotic cells
fbf-1(0); gld-1(0)	mitotic cells
lag-2(0); fbf-1(0)	meiotic cells
lag-2(0); gld-1(0)	mitotic cells

glp-1 → **GSC prolif.**

lag-2 → **GSC prolif.**

fbf-1 → **GSC prolif.**

gld-1 ⊣ **GSC prolif.**

lag-2 → ***glp-1*** → ***fbf-1*** → **GSC prolif.**

How do these genes work together?

Mutant	Phenotype
glp-1(0)	meiotic cells
glp-1(gf)	mitotic cells
lag-2(0)	meiotic cells
fbf-1(0)	meiotic cells
gld-1(0)	mitotic cells
glp-1(gf); lag-2(0)	mitotic cells
glp-1(gf); fbf-1(0)	meiotic cells
glp-1(0); gld-1(0)	mitotic cells
fbf-1(0); gld-1(0)	mitotic cells
lag-2(0); fbf-1(0)	meiotic cells
lag-2(0); gld-1(0)	mitotic cells

glp-1 → **GSC prolif.**

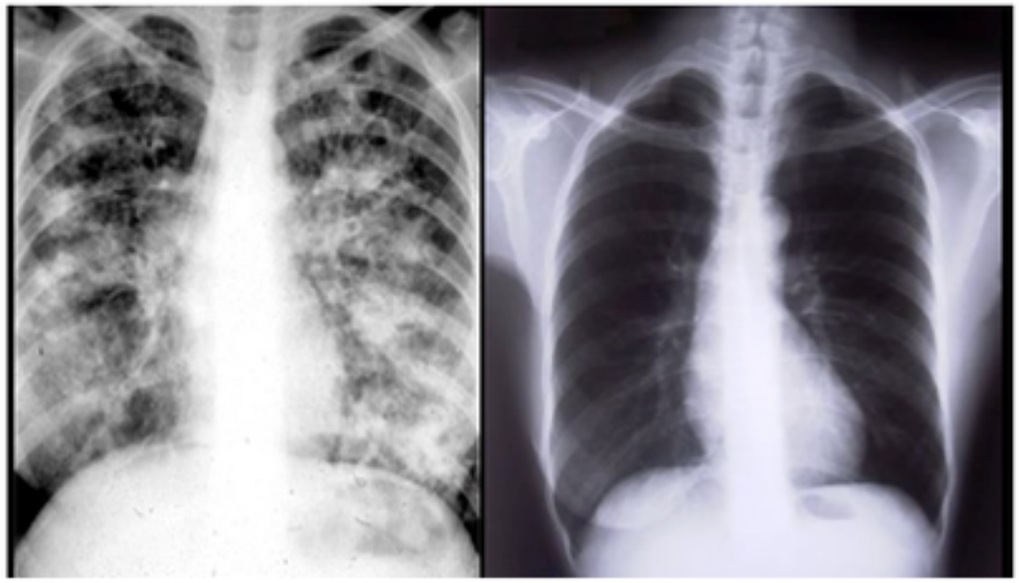
lag-2 → **GSC prolif.**

fbf-1 → **GSC prolif.**

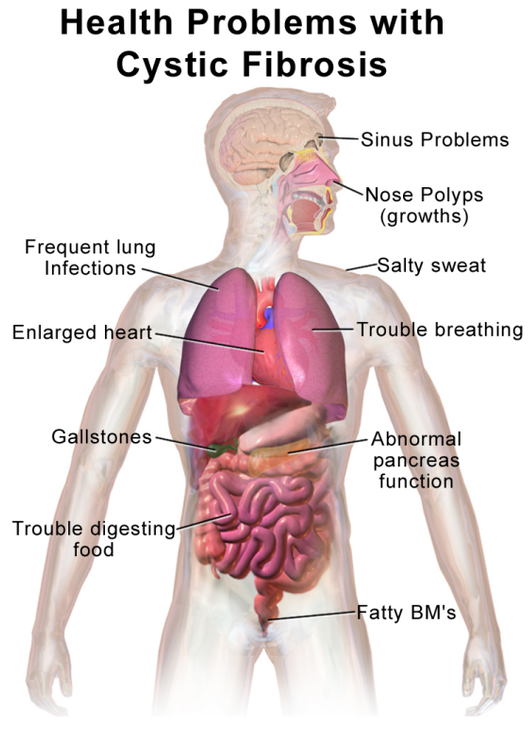
gld-1 ⊣ **GSC prolif.**

lag-2 → ***glp-1*** → ***fbf-1*** ⊣ ***gld-1*** ⊣ **GSC prolif.**

What about cystic fibrosis and today's topic?

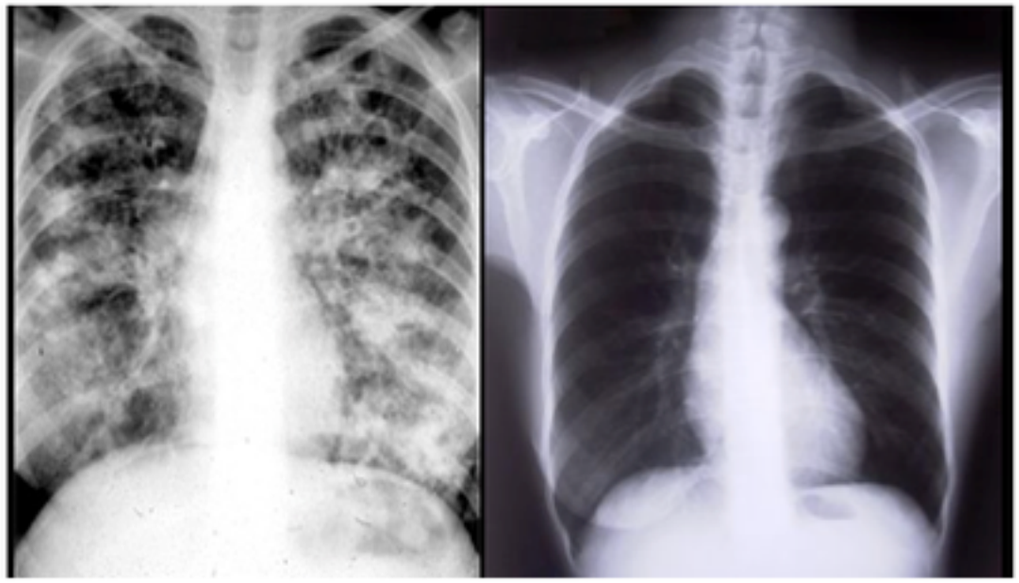


Cystic Fibrosis Lung Healthy Lung

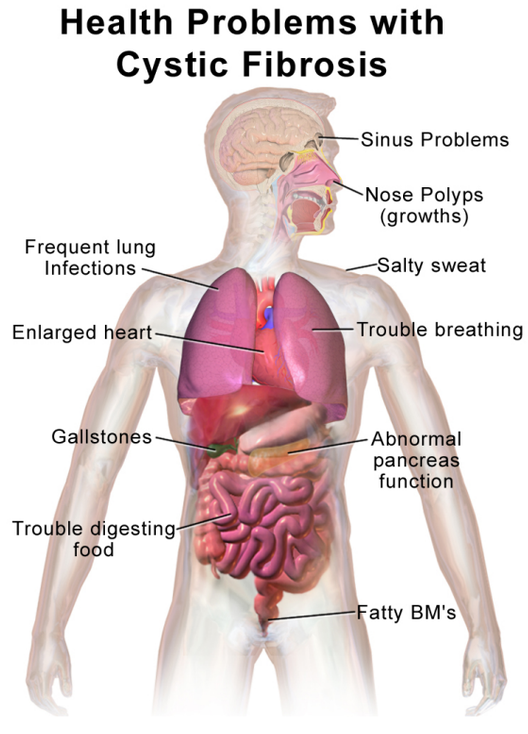


1. Autosomal recessive disorder
2. Not caused by chromosomal aberrations or meiotic NDJ
3. Mapped to chromosome 7
4. Mutations in CF gene are null or hypomorphs
5. Compound heterozygosity (failure to complement) is common

What about cystic fibrosis and today's topic?



Cystic Fibrosis Lung Healthy Lung



What data do we need to understand genetic interactions with the CF disease phenotype?