Welcome to the Third Genetics Exam! (The aftermath)

(Fall 2000)

Scoring

Your exam will have two numbers near the bottom left of your answer sheet. The first is the raw score, the sum of the number of points you got for each question. The highest number possible was 121, but we threw out your worst questions, up to a total of 10 points. The second (circled) number is the normalized score, calculated according to the formula that will appear in full below once we've graded all of the exams.

$$\text{normalized score} = 75 + 20 \cdot (\text{raw score} - 39.7)/69$$

The purpose of this complicated formula is to put the scores in the range of 50 to 100, where 90-100 is A, 80-90 is B, etc. The factors were chosen so that the normalized scores correspond to our perception of what constitutes an A and so forth. In this way, you know how this and all of your exam grades contribute to your final grade. There was no curve in this exam nor will there be in any future exam or for the final grade.

The Questions

2. (1 pt) True/false: You realize that Thanksgiving is less than 12 days away, and if you just take it one day at a time everything will be OK, and the sun shines behind every cloud.

97.4% of you agreed with the proposition. The remainder found fault with it, perhaps noting the time of day and that direct line from their seat to the nearest cloud would not pass through the sun.

3. (2 pts) As judged by the examples presented in this course, gene expression is regulated to a great extent at the level of:

A. Transcriptional initiation
B. Translational elongation
C. Transpositional termination
D. Transcendental meditation

There have been many examples presented in this course of regulation at the level of transcriptional regulation. Those who may have guided events by transcendental meditation have not stepped forward.

4. (9 pts) F'*lac* plasmids of different genotypes are mated into *E. coli* of different genotypes, as shown below. For each resulting strain, predict both the ß-galactosidase phenotype (**I** if ß-galactosidase can be induced by IPTG, **C** if activity is constitutive, and **N** if there is no activity under any circumstances) and the growth phenotype (**Lac**$^+$ if the strain can grow on lactose as the sole carbon source and **Lac**$^-$ if it cannot). If a genotype is not given for a gene or element, then it is presumed to be wild-type (+).An i^S gene encodes a repressor that is unable to bind allolactose. "*rbs*" signifies "ribosome binding site".

4a. $i^+ z^- y^-$ F'($i^- z^+ y^-$) **I Lac$^-$**

First check the transacting factors. Repressor is made -- doesn't matter from which gene. Let it bind to the operators. Both operators OK so low expression from both operons. Add IPTG, repressor goes away. ß-gal expressed from F' operon, but Lac permease expressed from neither since both genes are defective. Therefore, lactose can't enter the cell, hence no growth on lactose

4b. $i^+ o^c z^+ y^-$ F'($i^S z^- y^+$) **C Lac$^-$**

First check the transacting factors. Repressor is made, two kinds: normal and super (noninducible). Let them bind to the operators. One operator is defective, so no repressor binds. That operon then is on constitutively, producing ß-gal. The other operon is off. Add IPTG, normal repressor goes away, but super repressor is right there to take its place, so the chromosomal operon remains and the F' operon remains off. End result, no *y* gene that is being expressed, hence no lac permease and no growth on lactose.

4c. $i^+ rbs^+ z^- y^+$ F'($i^- rbs^- z^+ y^-$) **N Lac$^-$**

First check the transacting factors. Repressor is made -- doesn't matter from which gene. Let it bind to the operators. Both operators OK, so low expression from both operons. Add IPTG, repressor goes away. Transcription from both operons, but ribosomes can't bind to the transcript from the F' gene since the ribosome binding site (*rbs*) is defective. So no ß-gal from that source. The chromosomal operon has a defective *lacA* gene, so no ß-gal from that source either. No ß-gal means no growth on lactose.

5. (12 pts) Consider the section in your textbook on positive control of the *lac* operon (pp.403-404) in light of Fig. 1 on the next page. For each of the statements below taken from the book, provide two responses: (1) Indicate whether the data from the graphs, taken together, is supportive (**S**), contradicting (**C**), or uninformative (**U**) with respect to the entire statement. (2) If all the graphs are supportive or uninformative, indicate which graph (**A, B, C,** or **D**) is strongest in support. If at least one contradicts the statement, indicate which graph is strongest in opposition. If none are supportive or contradicting, draw a happy face.

I wish I could take back this question. It's clear that people interpretted it in a variety of ways. I had intended that you take the given genotype of the strain into account but consider what the graphs say about wild-type *E. coli*. I intended that each statement be interpreted narrowly. In light of the confusion, I gave partial credit of some sort to any answer, effectively reducing the weight of the question.

Many of you ignored the genotype of the strain. The *L8* mutation renders the *lac* operon oblivious to CRP, and the *uv5* mutation increases expression of the *lac* operon despite the failure of CRP to bind. This makes a huge difference in interpreting the graphs.

5a. (Par.1,Sent.3) *If both lactose and glucose are present, synthesis of ß-galactosidase is not induced until all the glucose has been utilized.* **S,A** or **U,☺**

Graph A shows that if both lactose and glucose are present, ß-gal is not unduced until midway through the curve, plausibly when glucose has been exhausted. Of course, the strain is not wild-type, but if this complicated phenomenon can occur with the mutant, I'm prepared to believe it could also with wild-type *E. coli* (and of course it can). Notice the statement says nothing regarding how the phenomenon is produced. I gave full credit for either Graph A supporting the statement or all graphs being uninformative.

Graphs B and C certainly can't be cited in opposition, because they're just what you'd expect from an L8 UV5 mutant -- unrestrained high expression in the presence of an inducer.

5b. (Par.3,Sent.1) *When glucose is present in high concentrations, the cAMP concentration is low…* **U,☺**

No graph says anything at all regarding cAMP concentration, hence they are uninformative in this regard. Any inference you make regarding cAMP concentrations presumes the truth of some model. Graph B describes the behavior of a mutant defective in CRP, but that says nothing about cAMP concentrations.

5c. (p.403, second to last line) *We now know that when a bacterium is exposed to glucose. . . cAMP is no longer available to bind to the CAP. Therefore, the unoccupied CAP does not bind to the CAP site. This causes the transcription [of the lac operon] to decrease.* **C,A** or **C,D**

What would it take to contradict this statement? Well, suppose you showed that transcription of the *lac* operon decreases when glucose is present, but not because of the comings and goings of CAP. That's what Graph A says, since it comes from a strain that does not bind CAP owing to the L8 mutation. Or (less strongly in my

opinion) suppose you showed that increasing something that should have no effect on CAP binding alters transcription of the *lac* operon. That's what Graph D says.

Graphs B and C are perfectly compatible with the statement, **so long as you remember that the graphs represent the behavior of an L8 UV5 mutant.** According to the standard model (that in the book), ruining the CAP binding site and increasing the strength of the promoter (the effects of the L8 and UV5 mutations) should produce a *lac* operon that is on or off at the pleasure of the Lac repressor. Therefore, in the presence of IPTG (Graph B) or lactose (Graph C), expression of ß-gal should be high, and so it is.

5d. Presuming the data of Fig. 1 to be accurate and broadly reflective of reality, is the model shown and described in the text the true basis for the diauxic effect?

If you found any graph above to be contradictory, then you should answer no.

6. (16) Reconsider Fig. 1 in light of the hypothesis depicted in Fig. 2, both on the next page. Only part of the model is shown in Fig. 2, that which is pertinent to the questions below.

6a. Indicate for each of the four graphs (panels **A** through **D**) whether it is supportive (**S**), contradicting (**C**), or uninformative (**U**) with regards to the hypothesis. In each case, explain your answer with respect to the most salient feature of the graph (no more than 20 words for each answer).

Graph A: (S) When glucose enters the cell, phosphate from IIA~P is transferred to glucose, leaving IIA unphosphorylated. The protein in that form inhibits the Lac permease. Since lactose cannot enter the cell, the *lac* operon remains repressed. When the supply of glucose is exhausted, IIA remains phosphorylated and the Lac permease becomes functional. Lactose enters and induces the *lac* operon. The level of ß-galactosidase rises and growth, temporarily halted with the consumption of glucose, resumes.

Graph B: (S) IPTG can enter the cell despite the inhibition of Lac permease, because it goes directly through the membrane. Therefore, the *lac* operon is induced at all times and ß-galactosidase is uniformly high. The absence of a diuaxic lag in growth can be explained either because: (a) ß-galactosidase and Lac permease are already present and ready for the moment that glucose is exhausted and the inhibition to the permease is lifted, or (b) induction of the *lac* operon by IPTG increases the level of Lac permease beyond the ability of IIA to inhibit it.

Graph C: (S) The loss of *crp* means that there is no CRP to bind to the regulatory site upstream from *ptsG*. As a result, there should be a drop in expression of the glucose permease. The failure of glucose to enter through the PTS permease means that IIA will remain phosphorylated, Lac permease will remain uninhibited, and lactose will enter the cell to induce the *lac* operon. Thus, ß-galactosidase levels should be uniformly high, and there should be no diauxic lag in growth, because lactose is available from the beginning.

Some observant souls noted that growth did not extend as far in Graph **C** as in the other graphs. This is what you would expect if only lactose is being utilized and only enough lactose was provided to support that amount of growth. However, we

don't know what happened to growth beyond the last point provided (it may have continued), and we don't know how much lactose was in the growth medium.

Graph D: (S) This is the toughest one, since the graph looks like neither Graph **A** (intact diauxic effect) nor Graphs **B** and **C** (obliterated diauxic effect). According to the model, unphosphorylated protein IIA does not act as an enzyme, permanently altering the Lac permease, but instead physically binds to it. Expressing more permease must therefore increase the amount of permease uninhibited at a given moment. Suppose that a little more Lac permease is uninhibited than usual in the presence of glucose, though much less than in the absence of glucose. Then a little lactose will trickle in and induce *lacZ* just a bit… and induce *lacY* as well! So now there's a little more Lac permease present and a little more of it uninhibited. So more lactose trickles in, and so forth. The observed results, rising ß-galactosidase activity, is a reasonable expectation.

6b. Presuming the data of Fig. 1 to be accurate and broadly reflective of reality, is the model shown and described in Fig. 2 the true basis for the diauxic effect?

The proper answer to this depended on your answer to 6a. If you found that at least one graph contradicted the expectations of the model, then you should have concluded that the model does not describe the true basis for the diauxic effect. On the other hand, if you found that all the graphs were consistent with the model, then…does that mean the model is correct? No. The model in the book matched available data for a while too. When contradicting data came along it had to be discarded. The model shown in Fig. 2 currently matches available data, but it may also prove to be wrong.

3. (2) The monumental work of a 19th century monk resulted in the enunciation of:

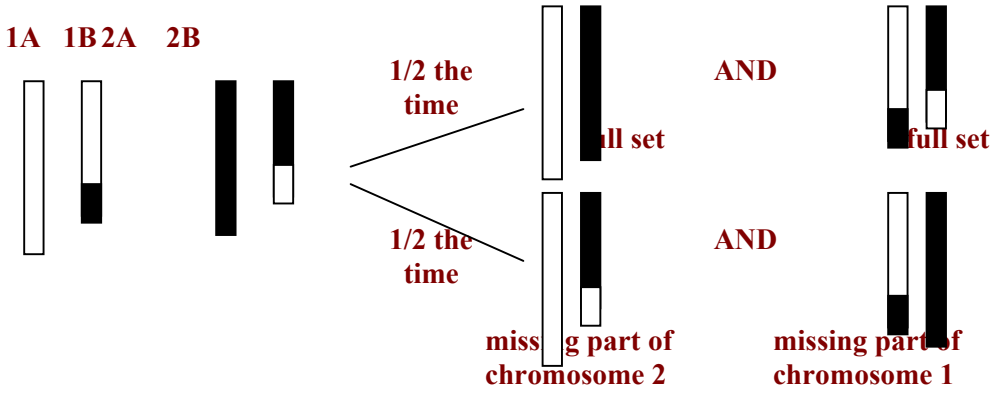
A. *Mendel's Principle of Independent Assortment*
B. *Morgan's Postulate of Chromosomal Recombination*
C. *Einstein's Theory of Special Relativity*
D. *The monk took a vow of silence, so we'll never know*

Most of you correctly identified **A**. Einstein, of course, was not a monk.

4. (2) A diploid organism has the genotype DdEEggHh. Assuming that each of the genes on a separate chromosome pair, what proportion of the organism's gametes will carry the genotype DEgh?

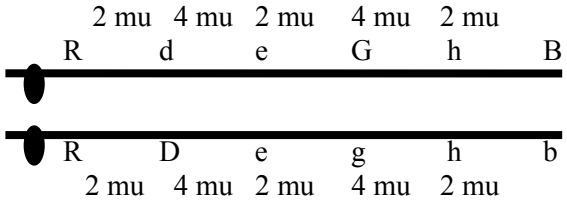
P(DEgh) = P(D from Dd) x P(E from EE) x P(g from gg) x P(H from Hh)
= 1/2 x 1 x 1 x 1/2
= 1/4

5. (4) A diploid organism (2N=4) is phenotypically wildtype even though it inherited normal chromosomes from one parent and a balanced translocation from its other parent as shown below. When this individual matures and makes gametes of its own, what proportion of its gametes will carry a full haploid set of genetic information? If you had to make any assumptions, please state them in 30 words or less along with your answer.

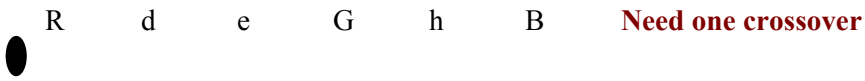


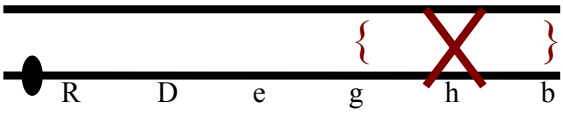
Therefore, 2 out of 4 possible gametes, or 1/2, carry a full set of genetic information, if I assume that the balanced translocation did not break up a gene.

6. (8 pts) A diploid organism has the following genotype for one of its homologous chromosome pairs (with the map units between genes shown).



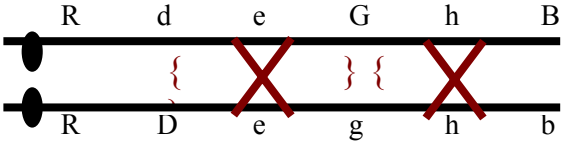
a. On the replica of the chromosome pair shown on the answer sheet, draw the minimal number of recombinations needed to get a gamete with RdeGhb.





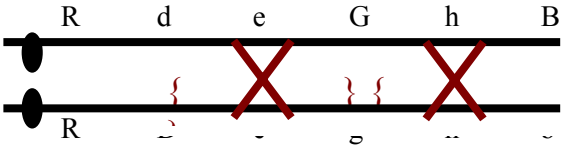
somewhere between the two brackets.

b. On the replica of the chromosome pair shown on the answer sheet, draw the minimal number of recombinations needed to get a gamete with RDeGhb.



Need two crossovers, each somewhere between the corresponding two brackets.

c. What proportion of the organism's gametes will be RDeGhb? Please show your equation along with your answer. (hint: think about the meaning of a map unit)



P(RDeGhb) = P(R-D) x P(D-G) x P(G-b) x 1/2
= 0.98 x 0.06 x 0.06 x 1/2
= 0.001764 or 0.0018

7. (5 pts) You are given an unknown T4 rII- mutant. Given your mastery of Lab #4, you carry out complementation and recombination tests using some of the same tester strains from Lab #4 (the location of the deletions in the tester strains are shown on your answer sheet). From the data you collect below, determine the area within which the unknown mutation must lie and state whether it is a point mutation or a deletion mutation.

Complementation Tests:

unknown + tester 33 No Lysis! **unknown has mutation in rIIA**
unknown + tester 34 No Lysis! **unknown has mutation in rIIB**

So, mutation impacts both genes. Only a deletion could do that.

Recombination Tests:

unknown x tester 32 No plaques on 10^{-1}, 10^{-2}, or 10^{-3}
deletion in unknown overlaps deletion in 32
unknown x tester 33 A few plaques on 10^{-1}, no plaques on 10^{-2} or 10^{-3}
deletion in unknown <u>does not</u> overlap the deletion in 33
unknown x tester 34 No plaques on 10^{-1}, 10^{-2}, or 10^{-3}
deletion in unknown overlaps deletion in 34
unknown x tester 35 A few plaques on 10^{-1}, no plaques on 10^{-2} or 10^{-3}
deletion in unknown <u>does not</u> overlap the deletion in 35
unknown x tester 36 No plaques on 10^{-1}, 10^{-2}, or 10^{-3}
deletion in unknown overlaps deletion in 36

So deletion in the unknown must range from the right end of rIIA (because it does not complement 33), without overlapping 33 to at least the left end of 34. The fact that only a few recombinants were found in the 36 cross tells us that the right end of the deletion in the unknown must extend further to the right, probably past the right end of 34.

8. (15 pts) The classic true breeding "High Jumper" fleas have a short football-shaped thoraxand very long hind legs as compared to their other legs. The recently introduced true breeding "High Stepper" fleas have an elongated thorax and their hind legs are just as short as their other legs. In an attempt to break into the small (pun intended), but lucrative flea circus market, you breed virgin "High Jumper" females with "High Stepper" males. The F1 progeny are a great disappointment. All of them are "High Jumpers" with a short football-shaped thorax and long hind legs. Undaunted, you selfcross the F1 progeny and get the following F2 progeny:

Number	Phenotype
7352	High Jumpers (short football-shaped thorax, long hind legs)
2352	High Steppers (elongated thorax, hind legs just as short as others)
148	High Stepper/Jumpers!! (elongated thorax, long hind legs)
148	Low Crawlers!!! (short football-shaped thorax, hind legs just as short as others)

a. What is the dominant form of each trait?

short football-shaped thorax and long hind legs

b. What are the genotypes of the the original parent strains?

TTHH x tthh

c. What would be the expected number of each F2 phenotypic class based on a hypothesis of a typical Mendelian dihybrid cross with independent assortment?

9/16 of 10,000, or 5625 T-H- High Jumpers
3/16 of 10,000, or 1875 T-hh Low Crawlers
3/16 of 10,000, or 1875 ttH- High Stepper/Jumpers
1/16 of 10,000, or 625 tthh High Steppers

d. Set up the proper chi-squared test to determine your confidence in the independent assortment hypothesis. You do not have to show the final calculated value, but rather just the initial equation with the proper numbers. Based on your equation, derive a rough estimate of what your chi-squared value will be and use that estimate to draw a conclusion concerning the hypothesis (conclusion in 15 words or less, please).

chi square $= \frac{(7352-5625)^2}{5625} + \frac{(148-1875)^2}{1875} + \frac{(148-1875)^2}{1875} + \frac{(2352-625)^2}{625}$

= ~500 + ~1000 + ~1000 + ~4800

= ~7300 WAY OFF THE CHART (P Value <<< 0.001)

No confidence in hypothesis of independent assortment.

e. You take one of your F1 females and mate it with a High Stepper male. Use the testcross progeny data below to draw as many additional conclusions as you can (in 20 words or less).

Number	Phenotype
4854	High Jumpers (short football-shaped thorax, long hind legs)
4846	High Steppers (elongated thorax, hind legs just as short as others)
151	High Stepper/Jumpers!! (elongated thorax, long hind legs)
149	Low Crawlers!!! (short football-shaped thorax, hind legs just as short as others)

(1) T and H genes are definitely linked, because testcross progeny are not in 1:1:1:1 ratio.

(2) Map distance between T and H genes = % recombinants
= (151+149) x 100% = 300 x 100% = 3 m.u.
(4854+4846+151+149) 10,000

9. (10 pts) You are working with three true breeding *Drosophila melanogaster* mutant strains: tiny eyes (TE), bristleless (BR), and leg-like antennae (LA). Your job is (a) to determine if the three genes lie on the same chromosome or on different ones, and (b) to determine the map distance between any genes on the same chromosome. You have two options. You can work with dihybrid crosses or you can work with a 3-point cross. Both options give the same answer.

Option #1: Dihybrid Crosses

(1) Parents: tiny eye females
x bristleless males
F1: all wildtype
tiny eye and bristleless are recessive
F1 females x tester males
progeny: 213 bristleless
210 tiny eye
91 tiny eye, bristleless
86 wildtype
recombinants are wt and double mutant
m.u. = (91+86) x 100% = 29.5
(213+210+91+86)

(2) Parents: leg-like antennae females
x tiny eyed males
F1: all leg-like antennae
tiny eye and normal antennae are recessive
F1 females x tester males
progeny: 152 tiny eye
150 leg-like antennae
50 wildtype
48 leg-like antennae, tiny eye
recombinants are wt and double mutant
m.u. = (50+48) x 100% = 24.5
(152+150+50+48)

(3) Parents: bristleless females
x leg-like antennae males
F1: all leg-like antennae
bristleless and normal antennae are recessive
F1 females x tester males
progeny: 125 wildtype
125 bristleless
125 leg-like antennae
125 bristleless, leg-like antennae
recombinants are wt and double mutant
no linkage, progeny in 1:1:1:1 ratio
Given that tiny eyes is 29.5 m.u. away from bristleless and that tiny eyes is

Option #2: 3-Point Cross

Parents: wildtype females x tiny eye, bristleless, leg-like antennae males
F1: all leg-like antennae

F1 females x tester males
progeny: 241 wildtype
239 tiny eye, bristleless, leg-like antennae
138 tiny eye, leg-like antennae
137 bristleless
113 leg-like antennae
112 tiny eye, bristleless
10 tiny eye
10 bristleless, leg-like antennae
the least abundant progeny classes are the double recombinants, the only gene order that works is br-te-la

% recombinants for tiny eye and bristleless = (137+138+10+10)x100 / 1000
= 29.5

% recombinants for tiny eye and leg-like antennae = (113+112+10+10)x100 / 1000
= 24.5

% recombinants for bristleless and leg-like antennae =
(138+137+113+112 +10+10+10+10)x100 / 1000
= 54
Why did we add 10+10+10+10?

24.5 m.u. away from leg-like antennae, all three genes must be on the same chromosome. However, the order has to be such that bristleless and leg-like antennae are ≥ 50 m.u. apart. The only order that works is:

br — te — la
29.5 24.5

54

Because these numbers reflect double recombinants, so they are truly recombinant between bristleless and leg-like antennae but they have two recombinations each. How did I know that? The gene order!

10. (12 pts) Females who carry either a defective allele in either of two genes, *BRC1* or *BRC2,* are predisposed to breast cancer. At least one wildtype *BRCA1* allele and one wildtype *BRCA2* allele are required for viability (embryos homozygous for either mutation do not complete development [Suzuki et al (1997) Genes Devel 11:1242-1252], but it is possible to be heterozygous at both *BRC1* and *BRC2* [Tsongalis et al (1998) Arch Path Lab Med 122:548-550]. The frequency of defective alleles vary considerably amongst different subpopulations. In females diagnosed early with breast cancer who can trace their roots to Ashkenazi Jews, the frequency of the $BRC1^-$ allele is 21% [FitzGerald, et al. (1996) New Engl J Med 334:143-149]. Suppose the frequency of the $BRC2^-$ allele in this same population is 10%.

A patient comes to you, a genetic counselor, for advice. Her mother was diagnosed at a very early age with breast cancer. She describes herself as an Ashkenazi Jew and wants to know what are the chances that she is at risk. You judge that she is at risk if she carries either of the two alleles. What probability do you give her? (Show equations)

I think this was the most complicated question on the exam. Let's take it apart.

1. **Patient wants to know her risk of getting breast cancer. (given)**
2. **Translation: Does she carry either of two alleles, $BRC1^-$ or $BRC2^-$? (given)**
3. **Patient describes herself as Ashkenazi Jew. (given)**
4. **Patient's mother probably would do the same. (reasonable guess)**
5. **Mother was diagnosed at an early age with breast cancer. (given)**
6. **21% of female Ashkenazi Jews diagnosed early with breast cancer have $BRC1^-$. (given)**
7. **10% of female Ashkenazi Jews diagnosed early with breast cancer have $BRC2^-$. (given)**

   NOTE: The question makes plain that it is possible to get breast cancer even if a female carries only wild-type alleles. Knowing that the mother had breast cancer does NOT tell you her genotype.
8. **The mother could not be either $BRC1^-$ $BRC1^-$ or $BRC2^-$ $BRC2^-$ because those genotypes are not viable. (given)**
9. **The mother could be $BRC1^+$ $BRC1^-$ $BRC2^+$ $BRC2^-$. (given)**
10. **The father is irrelevant. Early onset of breast cancer is very rare (look around), so the mutant alleles must be relatively rare. A person who is not part of a population**

at risk (mother, an Ashkenazi Jew, had early onset breast cancer) is unlikely to carry the allele.

OK, given all of this, what is the probability that the patient got either *BRC1*$^-$ or *BRC2*$^-$? I gave considerable credit to those of you who said that the patient might get affected in one of two ways:

The patient's at risk IF mother has *BRC1*$^-$ AND mother passes it
OR mother has *BRC2*$^-$ AND mother passes it

P(patient's at risk) = P(mother has *BRC1*$^-$)·½ + P(mother has *BRC2*$^-$)·½

Unfortunately, this ignores that the possibilities that the mother has *BRC1*$^-$ and *BRC2*$^-$ are not mutually exclusive, so you can't translate "OR" to "+". There were several ways of getting the best answer. I show two below.

<u>From mother's point of view</u>: The mother can have any of the following genotypes with the probabilities shown to the right:

(a) *BRC1*$^+$ *BRC1*$^+$ *BRC2*$^+$ *BRC2*$^+$	**(1 - 0.21) · (1 - 0.10)**	**= P(a)**
(b) *BRC1*$^+$ *BRC1*$^-$ *BRC2*$^+$ *BRC2*$^+$	**(0.21) · (1 - 0.10)**	**= P(b)**
(c) *BRC1*$^+$ *BRC1*$^+$ *BRC2*$^+$ *BRC2*$^-$	**(1 - 0.21) · (0.10)**	**= P(c)**
(d) *BRC1*$^+$ *BRC1*$^-$ *BRC2*$^+$ *BRC2*$^-$	**(0.21) · (0.10)**	**= P(d)**

because the probability of being wild type at a given locus is one minus the probability of carrying a defective allele. These are four mutually exclusive possibilities (a single person can't have two different genotypes), so I can consider each separately. In each case, the probability that the patient gains a mutant allele is:

P(mother has the genotype) · P(mother passes a mutant allele)

Adding up all the mutually exclusive possibilities, we get:

P(Patient's at risk) = P(a) · 0 + P(b) · ½ + P(c) · ½ + P(d) · □

Note that the probability of passing on a mutated allele is not the usual ½ in the last case, because there are two possible mutant alleles (do a Punnett square if you don't see where □ came from).

<u>From patient's point of view</u>: The patient will be at risk with any genotype <u>except</u> wildtype at both loci. So the probability that she's at risk is the probability that she is NOT wildtype at both loci:

P(Patient's at risk) = 1 - P(Patient is *BRC1*$^+$ *BRC1*$^+$)·P(Patient is *BRC2*$^+$ *BRC2*$^+$)

What's the probability that the patient is homozygous wildtype at a given locus? Again, it's the probability that she does NOT carry a mutant allele:

P(Patient is *BRC1*$^+$ *BRC1*$^+$) = 1 - P(Patient is *BRC1*$^+$ *BRC1*$^-$)

(Remember that she can't be homozygous mutant and be able to walk into your office). For her to be *BRC1*$^+$ *BRC1*$^-$, her mother has to carry the mutant allele and pass it on:

P(Patient is *BRC1*$^+$ *BRC1*$^-$) = P(mother is *BRC1*$^+$ *BRC1*$^-$)·P(she gives the allele)
(0.21) · ½

By the same reasoning:

P(Patient is *BRC2*$^+$ *BRC2*$^-$) = P(mother is *BRC2*$^+$ *BRC2*$^-$)·P(she gives the allele)
(0.10) · ½

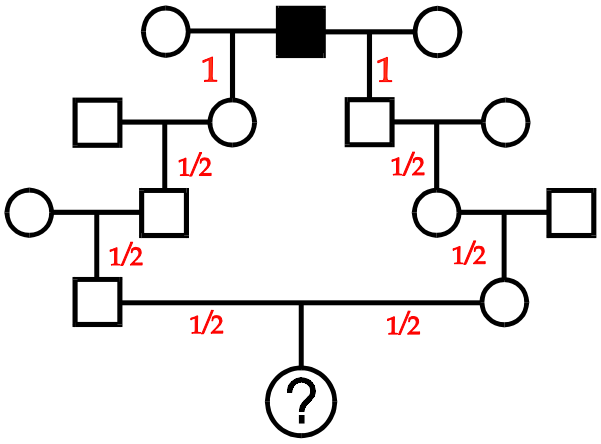
Putting it all together:

P(Patient's at risk) = 1 - [(1 - 0.21 · ½) · (1 - 0.10 · ½)]

This, I admit, was a very involved problem. I was pleased with the headway most of you made with it.

11. (8 pts) Although you won't find it in the family records, one of Brad's greatgrandfathers on his mother's side was the legendary but scandal-ridden Italian tenor, Bernardo Fettucini, known for his ability to shatter glass with his high E's. As chance would have it, Fettucini is also Asha's greatgrandfather, by another marriage. Piercing shrieks, a la Fettucini, is an autosomal recessive trait. Give the probability that daughter Ramsey Goodner (who at press time is still waiting in the wings) will have this rare trait (in not too long, Brad will tell us if she does or does not). In the space provided, draw the relevant pedigree along with whatever jottings may have helped you arrive at the answer.

In order for Ramsey to gain the trait, she must receive a mutant allele from both parents. And since the trait is rare, it is most likely to come from the common greatgrandparent. First of all, you got to get the pedigree right. Fetuccini was Brad and Asha's GREATgrandfather. Second, there is no question that as a homozygote, he passed on a mutant allele to all of his children, including the grandparents in question. The rest follows from the pedigree:

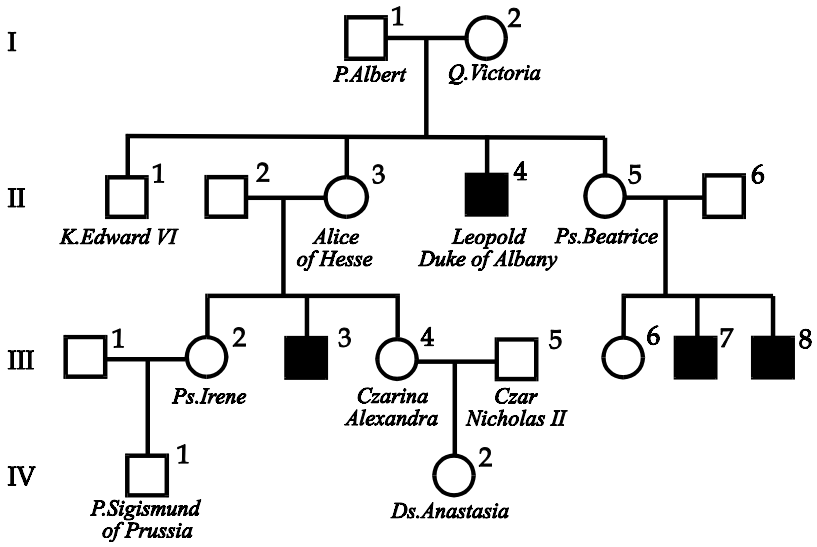


P(Ramsey gets the trait) = P(Brad has the allele) · P(Brad passes it)
P(Asha has the allele) · (Asha passes it)

Working backwards, the probability that Brad has the allele is ¼. Ditto for Asha. So:

P(Ramsey gets the trait) = (¼) · (½) · (¼) · (½) = 1/64

12. (12 pts) Examine the partial pedigree in the figure to the right of a family including many of the crowned heads of Europe. You will note that many of Queen Victoria's descendants were afflicted with hemophilia.

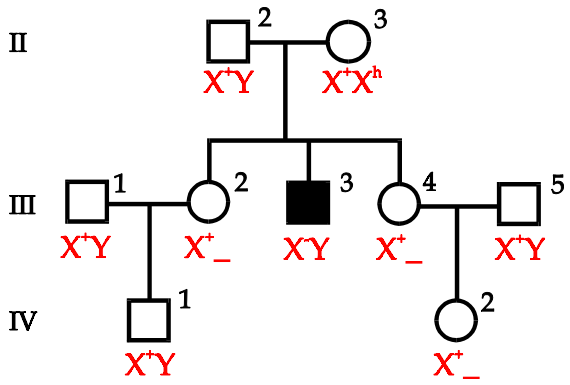


Partial pedigree of the descendants of Queen Victoria of Great Britain. Filled in symbols indicates symptoms of hemophilia.

12a. Describe the apparent mode of inheritance of the disease (e.g. autosomal dominant).

Ignoring the possibility that the trait is sex-limited (which doesn't sound very likely for a blood disease), dominance is ruled out because there are unaffected parents of affected children. Autosomal recessive transmission would require that four unrelated individuals (I.1, I.2, II.2, and II.6) all carry the allele -- not likely. Sex-linkage requires only that Queen Victoria carried the allele. So that wins.

12b. Write the genotypes of all individuals shown in the partial pedigree provided on the answer sheet, to the extent possible.



Given the answer to 12a, all the males must be wild type (X^+Y), except for III.3, who is affected, and all the females must have at least one wildtype allele ($X^+\_$). Only in the case of II.3 is her second allele known, because she had an affected progeny.

12c. It was common for marriages to be arranged amongst members of the extended royal family. Suppose that a union is contemplated between Prince Sigismund of Prussia and Anastasia, Duchess of Russia. What is the probability that a child of theirs would have hemophilia. Show all pertinent work.

P(child is affected) = P(IV.2 has X^h)·P(IV.2 gives it)·P(IV.1 has Y)·P(IV.1 gives it)

= P(IV.2 has X^h) · ½ · 1 · ½

P(IV.2 has X^h) = P(III.4 has X^h) · P(III.4 gives it)

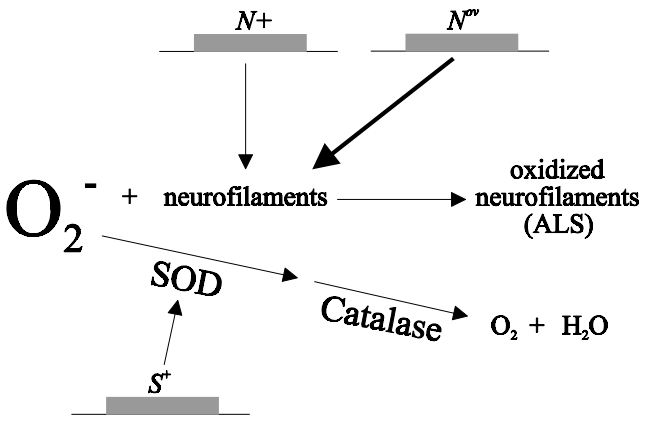
= ½ · ½ = ¼

so, plugging in:

P(child is affected) = ¼ · ½ · 1 · ½

= 1/16

13. (10 pts) At least in some cases, the neurodegenerative disease, amyotrophic lateral sclerosis (ALS), is caused by a genetic defect in the gene encoding superoxide dismutase (SOD). SOD, along with another enzyme called catalase, normally converts the toxic superoxide radical (O_2^-) to harmless molecular oxygen and water. When SOD is not present, the buildup of superoxide causes damage, eventually leading to neurodegeneration. Heterozygotes lack sufficient enzyme to prevent the condition.



Some believe that superoxide acts on neurofilaments, the primary protein of which (lets say) is encoded by the wildtype gene N^+. When neurofilaments are overproduced by the mutant allele N^{ov}, ALS is avoided, whether or not SOD is defective, presumably because more neurofilaments are produced than can be destroyed by superoxide.

To study the interaction of superoxide and neurofilaments, Kong and Xu [Neurosci Lett (2000) 281:72-74] employed a mouse model system. ALS symptoms were exhibited in mice carrying a defective SOD allele. They also made a mouse that carried an N^{ov} allele. Mice carrying

both had a delayed onset of ALS (let's call them normal). Suppose two such mice, each carrying one mutant S^- allele and one mutant N^{ov} were crossed, producing 96 progeny (it took a while).

13a. Which allele do you expect to act in a dominant fashion: S^+ or S^-?

Dominance is defined by the phenotype of heterozygotes. The question said, *"Heterozygotes lack sufficient enzyme to prevent the condition."* The clear implication is that heterozygotes have the same phenotype as the homozygote mutant, hence the mutant phenotype is dominant.

13b. Which allele do you expect to act in a dominant fashion: N^+ or N^{ov}?

Dominance is defined by the phenotype of heterozygotes. The question said, *"When neurofilaments are overproduced by the mutant allele N^{ov}, ALS is avoided…".* The implication is that neurofilament overproduction is achieved by a single N^{ov} allele. In the next paragraph, the question describes a mouse with "an *N^{ov} allele*" that avoids the disease, another indication that the mutant allele is dominant.

13c. What phenotypes do you expect in the 96 progeny and with what numbers?

The last sentence of the question describes a dihybrid cross:

$$S^+ S^- \; N^+ N^{ov} \;\; x \;\; S^+ S^- \; N^+ N^{ov}$$

Since S^- is dominant over S^+, and N^{ov} is dominant over N^+ then the relevant genotypes of the cross will be:

$$S^-\_ \; N^{ov}\_ \;\; : \;\; S^-\_ \; N^+ N^+ \;\; : \;\; S^+ S^+ \; N^{ov}\_ \;\; : \;\; S^+ S^+ \; N^+ N^+$$
$$9 \;\; : \;\; 3 \;\; : \;\; 3 \;\; : \;\; 1$$

Now all that's left is to evaluate the genotypes. The question said that "*Mice carrying both [an S^- allele and an N^{ov} allele] had a delayed onset of ALS (let's call them normal)",* so $S^-\_ \; N^{ov}\_$ are normal. Any mouse with normal SOD ($S^+ S^+$) is normal. The only mice with ALS at the usual time have the genotype of $S^-\_ \; N^+ N^+$. So the ratio of normal to affected mice is 13:1