Welcome to the Second 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.

\[
\text{normalized score} = 75 + 20 \cdot \frac{\text{raw score} - K_1}{K_2}
\]

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) Entering this exam, my mental state is:
   
   A. Eager, reverent, and hopeful.  
   B. Cautious and wary, but generally optimistic  
   C. Devoid of feeling  
   D. Drained and pessimistic  
   E. Suicidal  
   F. Whooppeee!  
   G. Other (specify)

14. (1) Repeat question 2, using the same choices to describe your mental state upon finishing the exam.

OK, here's who you were.
Judging A through E to represent a continual decline in optimism:

21 people grew more pessimistic
19 people didn't change
8 people grew more optimistic
31 people were incoherent

The chart to the above shows another way of looking at your emotional path through the exam. Consider A and B to be positive, D and E to be negative, and G to be interpreted on a case by case basis. The majority of people who exited positive, entered positive. Perhaps there's a lesson there.
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?

   $$P(DEgh) = P(D \text{ from } Dd) \times P(E \text{ from } EE) \times P(g \text{ from } gg) \times P(H \text{ from } Hh)$$
   $$= \frac{1}{2} \times 1 \times 1 \times \frac{1}{2}$$
   $$= \frac{1}{4}$$

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).

   - 2 mu   4 mu   2 mu   4 mu   2 mu
     R       d       e       G       h       B

   - 2 mu   4 mu   2 mu   4 mu   2 mu
     R       D       e       g       h       b

   Exam 2 Aftermath - 2
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.

\[ \begin{array}{ccccccc}
R & d & e & G & h & B \\
\{ & x & \} \\
R & D & e & g & h & b
\end{array} \]

Need one crossover 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.

\[ \begin{array}{ccccccc}
R & d & e & G & h & B \\
\{ & x & \} \{ & x & \} \\
R & D & e & g & h & b
\end{array} \]

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)

\[ \begin{array}{ccccccc}
R & d & e & G & h & B \\
\{ & x & \} \{ & x & \} \\
R & D & e & g & h & b
\end{array} \]

\[ P(\text{RD}e\text{Gb}) = P(\text{R-D}) \times P(\text{D-G}) \times P(\text{G-b}) \times \frac{1}{2} \]
\[ = 0.98 \times 0.06 \times 0.06 \times \frac{1}{2} \]
\[ = 0.001764 \text{ or } 0.0018 \]

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} \text{ 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} \text{ deletion in unknown does not overlap the deletion in 33 }
unknown x tester 34 No plaques on 10^{-1}, 10^{-2}, or 10^{-3} \text{ 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} \text{ deletion in unknown does not overlap the deletion in 35 }
unknown x tester 36 No plaques on 10^{-1}, 10^{-2}, or 10^{-3} \text{ 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 thorax and 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:

<table>
<thead>
<tr>
<th>Number</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>7352</td>
<td>High Jumpers (short football-shaped thorax, long hind legs)</td>
</tr>
<tr>
<td>2352</td>
<td>High Steppers (elongated thorax, hind legs just as short as others)</td>
</tr>
<tr>
<td>148</td>
<td>High Stepper/Jumpers!! (elongated thorax, long hind legs)</td>
</tr>
<tr>
<td>148</td>
<td>Low Crawlers!!! (short football-shaped thorax, hind legs just as short as others)</td>
</tr>
</tbody>
</table>

a. What is the dominant form of each trait?
   short football-shaped thorax and long hind legs

b. What are the genotypes of 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).

\[
\chi^2 = \frac{(7352-5625)^2}{5625} + \frac{(148-1875)^2}{1875} + \frac{(148-1875)^2}{1875} + \frac{(2352-625)^2}{625} \\
= \sim 500 + \sim 1000 + \sim 1000 + \sim 4800 \\
= \sim 7300 \text{ WAY OFF THE CHART (P Value <<< 0.001)}
\]

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).

<table>
<thead>
<tr>
<th>Number</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>4854</td>
<td>High Jumpers (short football-shaped thorax, long hind legs)</td>
</tr>
<tr>
<td>4846</td>
<td>High Steppers (elongated thorax, hind legs just as short as others)</td>
</tr>
<tr>
<td>151</td>
<td>High Stepper/Jumpers!! (elongated thorax, long hind legs)</td>
</tr>
<tr>
<td>149</td>
<td>Low Crawlers!! (short football-shaped thorax, hind legs just as short as others)</td>
</tr>
</tbody>
</table>

(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
= \(\frac{(151+149)}{10,000} \times 100\% = 300 \times 100\% = 3 \text{ m.u.}\)

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. = \(\frac{(91+86)}{213+210+91+86} \times 100\% = 29.5\)

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

**Option #2: 3-Point Cross**

1. 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 = \(\frac{(137+138+10+10)}{(137+138+10+10)} \times 100\)
m.u. = \( \frac{(50+48) \times 100}{152+150+50+48} = \frac{24.5}{1000} \)

(3) Parents: bristleless females
\( \times \) leg-like antennae males
F1: all leg-like antennae
bristleless and normal antennae are recessive
F1 females \( \times \) 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
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:

\[
\text{br} \quad \text{te} \quad \text{la} \\
29.5 \quad 24.5
\]

\[
54
\]

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

\[ P(\text{patient's at risk}) = P(\text{mother has BRC1-}) \cdot \frac{1}{2} + P(\text{mother has BRC2-}) \cdot \frac{1}{2} \]

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.

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

- (a) BRC1+ BRC1+ BRC2+ BRC2+ \[ (1 - 0.21) \cdot (1 - 0.10) = P(a) \]
- (b) BRC1+ BRC1- BRC2+ BRC2+ \[ (0.21) \cdot (1 - 0.10) = P(b) \]
- (c) BRC1+ BRC1+ BRC2+ BRC2- \[ (1 - 0.21) \cdot (0.10) = P(c) \]
- (d) BRC1+ BRC1- BRC2+ BRC2- \[ (0.21) \cdot (0.10) = P(d) \]

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:

\[ P(\text{mother has the genotype}) \cdot P(\text{mother passes a mutant allele}) \]

Adding up all the mutually exclusive possibilities, we get:

\[ P(\text{Patient's at risk}) = P(a) \cdot 0 + P(b) \cdot \frac{1}{2} + P(c) \cdot \frac{1}{2} + P(d) \cdot \frac{2}{4} \]

Note that the probability of passing on a mutated allele is not the usual \( \frac{1}{2} \) in the last case, because there are two possible mutant alleles (do a Punnett square if you don't see where \( \frac{2}{4} \) came from).

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

\[ P(\text{Patient's at risk}) = 1 - P(\text{Patient is } BRC1^+ BRC1^-) \cdot P(\text{Patient is } BRC2^+ BRC2^-) \]

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:

\[ P(\text{Patient is } BRC1^+ BRC1^-) = 1 - P(\text{Patient is } BRC1^+ BRC1^-) \]

(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:

\[ P(\text{Patient is } BRC1^+ BRC1^-) = P(\text{mother is } BRC1^+ BRC1^-) \cdot P(\text{she gives the allele}) \]
\[ (0.21) \cdot \frac{1}{2} \]

By the same reasoning:

\[ P(\text{Patient is } BRC2^+ BRC2^-) = P(\text{mother is } BRC2^+ BRC2^-) \cdot P(\text{she gives the allele}) \]
\[ (0.10) \cdot \frac{1}{2} \]

Putting it all together:

\[ P(\text{Patient's at risk}) = 1 - [(1 - 0.21 \cdot \frac{1}{2}) \cdot (1 - 0.10 \cdot \frac{1}{2})] \]

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:

\[ P(\text{Ramsey gets the trait}) = P(\text{Brad has the allele}) \cdot P(\text{Brad passes it}) \cdot P(\text{Asha has the allele}) \cdot P(\text{Asha passes it}) \]

Working backwards, the probability that Brad has the allele is \( \frac{1}{4} \). Ditto for Asha. So:

\[ P(\text{Ramsey gets the trait}) = \left( \frac{1}{4} \right) \cdot \left( \frac{1}{2} \right) \cdot \left( \frac{1}{4} \right) \cdot \left( \frac{1}{2} \right) = \frac{1}{64} \]

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.

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.

\[
P(\text{child is affected}) = P(\text{IV.2 has X}^h) \cdot P(\text{IV.2 gives it}) \cdot P(\text{IV.1 has Y}) \cdot P(\text{IV.1 gives it})
\]

\[
= P(\text{IV.2 has X}^h) \cdot \frac{1}{2} \cdot 1 \cdot \frac{1}{2}
\]

\[
P(\text{IV.2 has X}^h) = P(\text{III.4 has X}^h) \cdot P(\text{III.4 gives it})
\]

\[
= \frac{1}{2} \cdot \frac{1}{2} = \frac{1}{4}
\]

so, plugging in:

\[
P(\text{child is affected}) = \frac{1}{4} \cdot \frac{1}{2} \cdot 1 \cdot \frac{1}{2} = \frac{1}{16}
\]

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 (let’s say) is encoded by the wildtype gene N⁺. When neurofilaments are overproduced by the mutant allele N⁰v, 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 N⁰ 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 N⁰v 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 N⁰v?

Dominance is defined by the phenotype of heterozygotes. The question said, "When neurofilaments are overproduced by the mutant allele N⁰v, ALS is avoided...". The implication is that neurofilament overproduction is achieved by a single N⁰v allele. In the next paragraph, the question describes a mouse with "an N⁰v 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:

\[ S^+ S^- N^+ N^{0v} \times S^+ S^- N^+ N^{0v} \]

Since S⁻ is dominant over S⁺, and N⁰v is dominant over N⁺ then the relevant genotypes of the cross will be:

\[ S^- N^{0v} : S^- N^+ : S^+ S^- N^{0v} : S^+ S^+ N^+ N^{0v} \]

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 N⁰v allele] had a delayed onset of ALS (let’s call them normal)”, so S⁻ N⁰v 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.