Chapter 2
http://fire.biol.wwu.edu/trent/trent/IGA_10e_SM_Chapter_02.pdf

Note on 48: This trait shows variable expressivity with respect to the extent of blotching. When analyzing the data, a plant should be considered blotched even if there is limited amount of blotching

Chapter 6
http://fire.biol.wwu.edu/trent/trent/IGA_10e_SM_Chapter_06.pdf

Answers to extra problems

Problem 1
pleiotropic (multiple traits affected) sex-influenced, variably expressed

Problem 2
Answer is d: Note transmission through unaffected female in IVth generation.
(a) is eliminated by transmission of the trait via female IV.4 and by the III.1 who did not inherited the trait from his father;
(b) extremely unlikely,
(c) very unlikely and also female IV.4 is not consistent with this notion

Problem 3 Statement is true. See discussion of variable expressivity, incomplete penetrance and phenocopy in your text, relevant lecture material & the Genomes Unzipped reading assignment. The term genetic heterogeneity is used to describe situations where mutations in different genes can result in similar phenotypes.

Problem 4 a. pleiotropic

Problem 5 Most obvious feature of this pedigree is that only females are affected. Two possible explanations:
(1) Autosomal dominant inheritance with expression of the trait limited to females. This explanation seems unlikely because we would have expected to see the trait passed via unaffected males.
(2) X-linked dominant trait with homozygotes and hemizygotes inviable. This would explain the other striking feature of this pedigree which is that the trait is never passed via the male line. This explanation is probably the best.
Problem 6  No. See discussion of variable expressivity in textbook and lecture notes.  In the case of monozygotic twins, genetic background cannot explain the variable expressivity.

Problem 7
0.55 = 0.5 (genotypically wildtype offspring) + 0.05 (0.5 x0.1 offspring het for trait but doesn’t exhibit phenotype)

Problem 8  Answer is d: the D gene is a modifier

Problem 9
\[ \begin{array}{ll}
C & \text{incomplete dominance} \\
A & \text{variable expressivity} \\
I \text{ or } C & \text{polymorphic} \\
C & \text{X-linked dominant} \\
A & \text{pleiotropic} \\
A & \text{loss-of-function} \\
\end{array} \]

\[ \begin{array}{ll}
C & \text{haploinsufficient} \\
I & \text{incomplete penetrance} \\
A & \text{autosomal recessive} \\
I* & \text{sex-limited/sex-influenced} \\
\end{array} \]

* Since the parents are related, this could be a sex-limited, X-linked recessive trait, but this is not the simplest explanation. It could also be a sex-limited autosomal trait, but, again, there is no direct evidence one way or the other.

Problem 10
\[ \begin{array}{ll}
T & \text{[The mutant allele is pleiotropic]} \\
T & \text{[The mutant allele shows variable expressivity]} \text{ YES, not everyone shows both traits associated with the mutant allele} \\
F & \text{The mutant allele represents a polymorphism: NO, it is very rare} \\
F & \text{The transmission pattern is consistent with an X-linked dominant mutant allele showing incomplete penetrance (both traits taken together): NO, see left side of pedigree} \\
F & \text{The transmission pattern is consistent with an X-linked dominant mutant allele showing complete penetrance (both traits taken together).} \\
T & \text{The transmission pattern is consistent with an autosomal dominant mutant allele showing incomplete penetrance (both traits taken together).} \\
F & \text{The transmission pattern is consistent with an autosomal dominant mutant allele showing complete penetrance (both traits taken together).} \\
\end{array} \]

For the next set of questions assume that this pedigree shows the inheritance of a common set of traits -- such as red hair and freckles in a British population. Assume that these phenotypes result from a loss-of-function mutation in a gene coding for a receptor protein that controls melanin production. Indicate True, False or N (not enough information provided to assess). Indicate false, if any part of the statement is false.

\[ \begin{array}{ll}
T & \text{The transmission pattern is consistent with autosomal recessive inheritance of a completely penetrant mutation (both traits taken together).} \\
\end{array} \]
The transmission pattern is consistent with autosomal recessive inheritance only under the condition of incomplete penetrance (both traits taken together). The mutant allele is pleiotropic. The mutant allele represents a polymorphism.

Problem 11: answer is b.

Problem 12 Be sure to review your lecture notes on the complicated relationship between genotype and phenotype. Since the penetrance is different in different populations, differences in genetic background (suppressor or modifier mutations) may influence the expression of the trait. For example, the gene pool of the outbred population (penetrance is 40%) may contain a suppressor mutation that in combination with the glaucoma mutation results in a normal phenotype. The gene pool of the inbred population may not contain that suppressor allele. It is also possible that there are environmental factors that influence the expression of the trait that are different for the two populations.
**Problem 13**

Parental              sluggish          X          wildtype (normal activity level)
                      H  H  r  r            h⁺  h⁺  R⁺  R⁺

F1                        all animals are hyper
                      H  h⁺  R⁺  r

F1 Cross A  F1  hyper  X  wildtype (parental strain)
                      H  h⁺  R⁺  r

F2  ½ hyper  ½ wildtype
                      H  h⁺  R⁺  -

**Problem 14**  ANSWER discussed in class

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**Part A.**  Consult the information on pg 1 of the extra sheet. Define allele symbols (respecting allele symbol conventions), indicate dominance and specify the trait that each gene controls.

- **H** = Hyper (excess ligand)
- **h⁺** = normal ligand
- **R⁺** = normal receptor
- **r** = loss-of-receptor
- **rr** = sluggish  independent of the genotype at the ligand locus

H and R⁺ are dominant.

**Part B**  What type of gene interaction is operating here? Use proper terminology (no explanation required) epistasis  rr genotype is epistatic to the H gene.

**Part C**  Indicate genotypes for all crosses.
**Problem 15**

a. No, Chaplin could not have fathered this child. The father must have been either \(I^B i\) or \(I^b I^b\).

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>ABO Genotype (no complications)</th>
<th>Revised Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>woman</td>
<td>A</td>
<td>(I^A i)</td>
</tr>
<tr>
<td>Chaplin</td>
<td>O (not A or B)</td>
<td>(i i)</td>
</tr>
<tr>
<td>child</td>
<td>B</td>
<td>(I^B i)</td>
</tr>
</tbody>
</table>

b. Epistasis – a recessive loss-of-function mutation in the \(H\) gene would be epistatic to the ABO gene.

c. The \(H\) gene codes for the \(H\) enzyme which catalyzes a reaction whose end-product serves as the substrate for the \(A\) and \(B\) enzymes which produce the \(A\) and \(B\) antigens respectively. Therefore, a loss-of-function mutation \((h)\) in the \(H\) blocks this pathway upstream of the ABO gene and effective “masks” the genotypes at this locus. Student answer: Genes (alleles) \(A\) and \(B\) code for enzymes that need the product of the \(H\) enzyme as a substrate. If there is a mutation in the \(H\) gene and no \(H\) enzyme is formed it can mask the effects of \(A\) and \(B\) due to epistasis.

d. see above

e. \(\frac{1}{2}\) chance \(I^A I^B\) X \(\frac{3}{4}\) chance \(H^- = \frac{3}{8}\)

f. \(\frac{1}{4}\) chance \(hh\) X 1 (any genotype at the AB locus) = \(\frac{1}{4}\)

**Problem 16**

a. \(B & D\) Note that the cutoff between disease and normal phenotype is between 50% and 100%

b. \(C\) The gene haplosufficient since the cutoff between disease and normal phenotype is between 0% and 50% and within the disease range is the disease is variably expressed.

c. \(D\) Heterozyotes show a phenotype that is more limited than that exhibited by homozygotes.

d. recessive:

\(a^+ = \) wildtype allele \(\quad a^+ a^+ = 100\%\) activity
\(a = \) mutant allele with 50% activity \(\quad a^+ a = 75\%\) \(\quad a a = 50\%\)

since \(a^+ a = 75\%\) = No effect. Therefore, \(a\) is recessive to \(a^+\)
**Problem 17 Part A:** Propose a concise, title (one phrase or sentence) for this article. The title should summarize the gene interaction described in the text. *Be sure to be explicit as possible and use appropriate terminology.*

**STUDENT ANSWER:** *SUPPRESSION OF THE ALS DISEASE STATE IN NOX1 & NOX2 KNOCKOUT MICE*

**Part B** Indicate True, False or N (not enough information provided to assess). 3 pt each. If you choose N, indicate what additional information you would need.

**TRUE** Assuming all cases of ALS are genetically determined, the article implies that this disease state is genetically heterogeneous (or shows genetic heterogeneity).

*One sentence explanation/defense of your answer:*
The article states that mutations in the SOD gene account for 1-2% of ALS cases indicating that mutations in other genes are responsible for the majority of cases.

**TRUE** The studies described in the article suggest that there are other genes (in addition to Nox-1 and Nox-2) that can influence expression of the ALS mutation.

*One sentence explanation/defense of your answer:*
See last paragraph. The effect of the Nox-2 knockout on ALS differed in different strains of mice – probably due to differences in the genetic background.

*Student answer: Nox1 and Nox2 are described as two of “several” proteins that generate reactive oxygen species.*

**TRUE** Although not stated explicitly in the article, the results of the studies suggest that polymorphisms affecting the activity of the Nox-2 gene could result in variable expressivity or incomplete penetrance of SOD1 mutations in humans.

*One sentence explanation/defense of your answer:*
Assuming that the observations made using the mouse model extend to humans, then polymorphisms in the human Nox-2 gene that influence the level of activity of the NOx-2 protein are likely to affect the phenotypic outcome of a SOD1 mutation by paritally suppressing its pathogenic effect.

*Student answer: If polymorphisms in this gene do exist, then the study suggests that lower levels of Nox2 will lessen the severity of the phenotype produced by SOD1.*

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**Problem 18 Part A**

**T F N** The mutant DISC allele can be considered a polymorphism in the population described in this study. *One sentence defense of your answer:*
The text clearly states that the mutation was not found in 424 control individuals; even if we add in the genotype data from the pedigree, the frequency of the mutant allele is <1%.

**T F N** Based on this pedigree, The DISC1 gene must be autosomal.

*One sentence defense of your answer:*
Two observations exclude X-linkage:
- The mutant allele is passed from father II6 to son III5.
– daughters III 9 7&10 of II6 did not receive the mutant allele from their father

**T F N** The pedigree data suggest that the DISC1 gene is *haplosufficient*.

**One sentence defense of your answer:**

Note affected individuals are heterozygotes. Therefore, one normal copy of the gene is not “sufficient” to produce a normal risk of schizophrenia. **NOTE:** the fact that II6 is a het and does not show the trait, simply means that the genotype is incomplete penetrant.

**T F N** The DISC1 mutant allele is *incompletely* dominant to the wildtype allele.

**One sentence defense of your answer:**

Need to know what deletion homozygotes look like before we can assess

**T F N** Based on the text, the predisposition to schizophrenia is likely to be genetically heterogeneous. **One sentence defense of your answer:**

Yes, the text clearly states a prediction from the researchers that allelic variations in other genes in DISC1 related pathways may contribute to disease risk.

**T F N** The pedigree data suggest that other genetic risk factors for schizophrenia may be present in the people included in this study.

**One-two sentence defense of your answer. Be very specific as to which individuals are important here.**

The most persuasive arguments for other risk factors segregating in this population are that:

1. the trait is highly heritable
2. individual III #11 has schizophrenia but her side of the pedigree is presumably not segregating the specific risk allele under study
3. individual III #9 is known to not have the DISC mutation but none-the-less exhibits a schizotypal personality disorder

**Problem 18 Part B**

**a. Refer again to pg 2 of the extra sheet.** Briefly state the evidence for incomplete penetrance shown in this pedigree. **One sentence maximum. Be very explicit.**

Individual II 6 is het for the DISC mutation but does not exhibit any associated phenotypes

**b.** List the three categories of factors (as discussed in class) that interact to influence the expression of a trait. For each category give a **general description/explanation** (1-2 sentences). Then, for ONE of the categories (your choice) give a specific relevant example. Use proper terminology and complete sentences. You can use examples from the lectures, or from other courses, but hypothetical examples are fine and expected.

**MANY possible answers here – see lecture notes and problem sets**

**Problem 18 Part C**

**REVIEW** the lecture on model organisms. Need to talk about the practical and theoretical justification for using models and indicate that we share with mice most of our genes and our nervous systems (including signal transduction and neurotransmitter biochemistry) have much in common with other mammals