Bio393: Biomedical Genetics **Name:**_____
Problem Set #5
Due on Friday, May 10, 5 PM

Question 1:
Circle the correct answer.

(a) Which type of variant is easiest to map using family-based analyses?

1 - Rare variants with variable penetrance
2 - Common variants with variable penetrance
3 - Rare variants with high penetrance
4 - Common variants with high penetrance

(b) Which type of variant is easiest to map using population-wide analyses?

1 - Rare variants with variable penetrance
2 - Common variants with variable penetrance
3 - Rare variants with high penetrance
4 - Common variants with high penetrance

Question 2:
Genetic loci with large phenotypic effects are usually rare across populations.

(a) Provide an explanation for why.

Genetic loci with large phenotypic effects are rare because in most cases they deleteriously affect fitness. Decreased fitness means that alleles are less likely to get passed on and do not increase in frequency across populations.

(b) The variants that cause age-related macular degeneration have reached intermediate frequency in the human population. How do you think that large-effect variants (like those alleles) reach intermediate frequencies in humans?

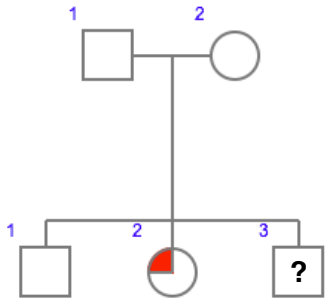
The variants that cause AMD likely do not affect fitness so they can be passed on and can increase in frequency across populations. AMD is age-related, so most people will have offspring before these alleles can affect fitness as well. Additionally, AMD (even at its most severe case) will not cause lethality. Blind people can still have offspring, and the alleles will persist in populations.

Question 3:
Recurring behavioral disorders were observed in some male members of a large pedigree extending over several generations. The males were mildly mentally retarded and, especially when under stress, were prone to repeated acts of aggression, including sex offenses, attempted murder, and arson. An X-linked gene, MAO, coding for the enzyme monoamine oxidase, which participates in the breakdown of neurotransmitters, was found to be defective in the affected men in this pedigree. Other researchers found abnormal levels of monoamine oxidase in some unrelated men with similar behavioral issues, even though the MAO gene was not defective in these cases. Does this evidence support the hypothesis that defective monoamine oxidase is responsible for the behavioral disorder? Please explain your answer.

The evidence is correlative within one population but not in the other population. It is possible that in the large family with the defective MAO gene that MAO is the causal gene underlying this behavioral trait. However, again, the evidence is only correlative. One would need to connect loss of MAO gene function using genetic experiments to this behavior. In humans, this goal is difficult if not impossible.

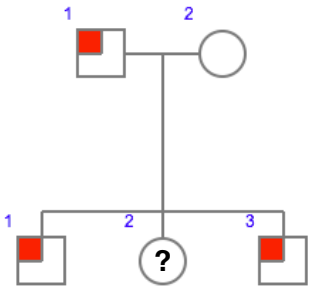
Question 4:
Each of the families below exhibits a different, extremely rare genetic disorder. Individuals expressing the trait (the disorder) are indicated by symbols with red sections. Assume that no new mutations have arisen in any of the individuals shown. Consider the following possible modes of inheritance: (i) X-linked recessive with complete penetrance, (ii) autosomal recessive with complete penetrance, (iii) autosomal recessive with 70% penetrance, (iv) autosomal dominant with complete penetrance, (v) autosomal dominant with 70% penetrance. For each pedigree state which, if any, of these five modes of inheritance are not possible. For the modes of inheritance that are possible, calculate the probability that the individual indicated by a "?" is affected.

(a)



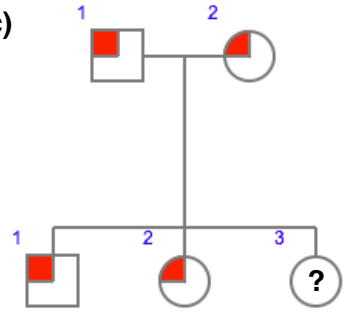
i. Not possible because individual I-1 is not affected.
ii. Possible, individual II-3 has a 1/4 chance of being affected or 1/2 of being a carrier
*iii. Possible, individual II-3 has a 1/4 * 7/10 chance of being affected or 7/40.*
iv. Not possible, neither parent is affected
*v. Possible, one parent must be a carrier but not fully penetrant. The probability that individual II-3 will be affected is 1/2 * 7/10 = 7/20*

(b)



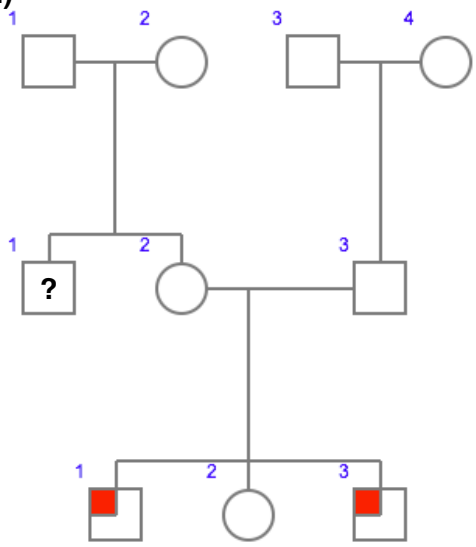
i. Possible if individual I-2 is a carrier. II-2 has a 1/2 chance of being affected
ii. Possible, same as i, 1/2 chance of being affected
*iii. Possible, because of penetrance the chance is 1/2 * 7/10 = 7/20*
iv. Possible, 1/2 chance of individual II-2 being affected
*v. Possible, same logic as iv except penetrance changes the chance to 1/2 * 7/10 = 7/20*

(c)



i. Possible, individual II-3 has 100% chance of being affected
ii. Possible, individual II-3 has 100% chance of being affected
iii. Possible, individual II-3 has 100% chance of inheriting the affected allele but a 7/10 chance of being fully penetrant so 7/10 chance overall
iv. Possible, because the disease is rare both parents are likely heterozygotes, individual II-3 has a 3/4 chance of being affected
*v. Possible, same logic as iv, because the disease is rare both parents are likely heterozygotes, individual II-3 has a 3/4 chance of being affected, but penetrance makes the chance 3/4 * 7/10 = 21/40*

(d)



i. Possible, individual II-1 has 1/2 chance of being affected
ii. Possible, but pretty unlikely both parents would have to be carriers. For a rare disease, it is highly unlikely.
iii. Possible, but pretty unlikely both parents would have to be carriers. For a rare disease, it is highly unlikely.
iv. Not possible, no affected individuals in generations I or II
*v. Possible, individuals in generations I or II would have to be not fully penetrant. Individual I-1 or I-2 could be a carrier and not penetrant for the disease. Because it is a rare disease, we expect that both would not be carriers. If one is a carrier, then II-1 has a 1/2 * 7/10 or 7/20 chance of expressing the disease.*

*However, we also do not know what side of the pedigree the allele conferring the dominant phenotype would come from, so we need to take into account that probability (1/2). 1/2 * 1/2 * 7/10 = 7/40*