**Chapter 5 Study Questions**

*Genetic Analysis: Genes, Genomes, and Networks in Eukaryotes*

1. The two most widely used starting points for cloning a gene are its map position and its expression pattern. Discuss what makes these the most convenient starting points, and the advantages and disadvantages of starting with each one.
2. You are a first year graduate student in a genetics lab. When you come into the lab, the principal investigator hands you a mutant strain, and says, “Come back tomorrow, and tell me how you would clone this gene.” Describe the strategy that you would use to begin to clone the gene responsible for each of the following mutant phenotypes. Assume that all of the mutant phenotypes are recessive and can be grown as homozygotes. You may also assume that you have access to all of the information and genetic strains and reagents that are widely used in that organism. However, at the time the analysis begins, you have only the mutant (and access to the genome databases), and no other information. Describe how you would clone the gene in each of the following scenarios.
   1. A yeast mutant that results in hyphal growth; that is, long filaments rather than discrete round colonies.
   2. A mutant in flies that results in crossing over in males but has no effect in females (Recall that males in Drosophila do not typically cross over during meiosis.)
   3. A mutant in worms that forms blisters on the cuticle. The cuticle is made of collagen.
   4. An Arabidopsis mutant that flowers much earlier than wild-type under normal lab or green house conditions.
   5. A mouse with a variegated coat color patterns (such as spots or blotches) rather than a solid black or brown color.
3. In the October 2011 issue of *PLoS Genetics*, Pierson et al. used whole-exome sequencing to identify the mutations responsible for a rare spastic ataxia-neuropathy syndrome. The paper and supporting information can be found at <http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1002325>, and you will need to access the paper to answer these questions. The paper is focused primarily on the phenotype and the particular gene, but our attention will be primarily on the methods used for the exome-sequencing approach, which is found in the Methods and in the Supporting Information.
   1. Figure 1A shows a pedigree of the family with two affected sons, who are not identical twins.
4. Recalling pedigree analysis from your introductory genetics course, what is the most likely mode of inheritance for this syndrome?
5. What is the probability that the next child born to this couple will be disease-free?
   1. Summarize the experimental strategy that yielded the results shown in Supplemental Table S2, as found under Supporting Information. Your summary should define the abbreviations used in the column headings and what the numbers mean. You should also include an explanation of why the numbers decrease as one reads from left to right from columns 2 through 6 (not including Total Protein Coding Exons Sequenced.)
   2. The numbers of candidate genes in Supplemental Table S3 are 71, 7 and 2, but these numbers do not appear anyway in Supplemental Table S2. What inference from the data was made that allowed the investigators to arrive at the numbers in Table S3 based on the numbers in Table S2?
   3. What further inferences led the investigators to conclude that AFG3L2 is the gene that is most likely responsible for this syndrome?
   4. In the analysis of Miller Syndrome described in the chapter, the affected children did not have the same mutation on each homologous chromosome, and were in fact heteroallelic for the mutations. In this example, the children have the same mutation on each homologous chromosome. Why did the authors expect that the affected children would be homozygous for the same mutation?
   5. What is the postulated mechanism by which this mutation results in this phenotype?
   6. The mutation in these boys appears to be a hypomorphic mutation, and is recessive. Null mutations in this gene are apparently dominant in their effects. How can this result be explained?