

Scenario B – Drug Metabolism

Background:

You are a medical research group studying drug metabolism in humans. Understanding the variability among humans in terms of how they metabolize drugs has a wide range of applications for the medical community, including helping with questions like: How much of a drug should be prescribed? When should a person take the drug? Should the person take the drug at all? What alternatives should be looked at, etc.? The gene CYP450 is known to be involved in the metabolism of 90% of commercially prescribed drugs. You decide to do a research study into the CYP450 gene activity in group of 250 patients using the CYP GeneChip microarray.

For your study, you are aware of 6 important alleles (versions) of the CYP450 gene. For simplicity's sake we shall call them allele #1 – 6. Each version of the gene has a different level of activity due to point mutations, base insertions or deletions. Past research has shown that the 6 alleles can be placed into three categories based on their activity (i.e., how much they influence drug metabolism) – Normal Activity, Reduced Activity, and Inactive. Here is the category that each allele is known to lead to:

Allele 1 – Reduced Activity	Allele 2 – Normal Activity
Allele 3 – Normal Activity	Allele 4 – Reduced Activity
Allele 5 – Inactive	Allele 6 – Inactive

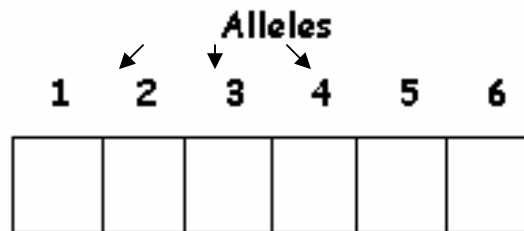
Remember, in most cases, everyone has two alleles for each gene and could be homozygous (two of the same alleles) or heterozygous (two different alleles). Thus, a person could have the genotypes such as 1/3, 2/5, 4/4, 3/6, or 5/5. In this case there are many possible genotypes – 21 in total. Your group decides to look into the different genotypes that exist predominantly in the population to help with the prescription of drugs. In other words, if people who do not metabolize drugs well have the genotype 5/6, then the doctor could adjust the prescription accordingly.

You want to find out what types of “metabolizers” have which type of genotypes. Recent research has shown there to be 4 categories of metabolizers (or four phenotypes): Poor Metabolizers (PM), Intermediate Metabolizers (IM), Full Metabolizers (FM), and Ultra Metabolizers (UM). UMs break down the drug so fast that the drug does not have sufficient amount of time to work for the person. PMs are unable to use the drug efficiently. IMs show a low level of metabolism, but more than PMs. FMs show a normal, full range of metabolism. This is the most satisfactory phenotype where the person is able to get the most from the drug.

To do your study, your group uses the CYP GeneChip microarray * to study the possible genotypes leading to the four phenotypes.

* Note: this Chip is based on the real chip used to study the CYP450 gene. It is known Roche's CYP450 GeneChip microarray (AmpliChip).

You study 250 patients. First, you administer Dextromethorphan (a cough suppressant) and take urine samples at specific times to determine how well they metabolize the drug. If they are a poor metabolizer you should find high levels of Dextromethorphan in their urine indicating that very little of the medicine has been metabolized. If they are ultra metabolizers there should be very little of the medication in their urine because most of it has been metabolized while in the body. This will allow you to determine which of the four phenotypic categories they belong to. Next, you take blood sample from which you isolate DNA. You prepare the sample and hybridize it to the chip in the normal manner. Reading of the chip signatures will be simplified to showing one feature for each allele (although typically multiple features are used for each allele). Here is a blank, sample data set:



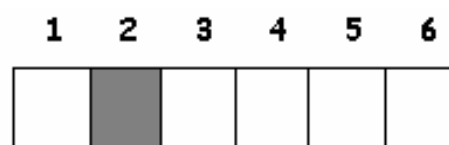
If a feature is shaded in, that means the particular allele is found in the DNA from that person. The one catch is that there is the possibility of a person containing more than two alleles in their genome. This mutation is known as gene duplication and is usually an error in replication during meiosis from the mother or father. Gene duplication usually leads to over expression of the gene due to the multiple copies. The codes for the different shades are as follows:

- Black - multiple copies of the allele (more than 2)
- Dark Grey – two copies of the allele
- Light Grey – one copy of the allele
- White – no copies of the allele

So, here are a few examples. The one on the left shows a person that has the genotype 4/5 and the one on the right shows a person that is 2/2 (homozygous for allele 2):



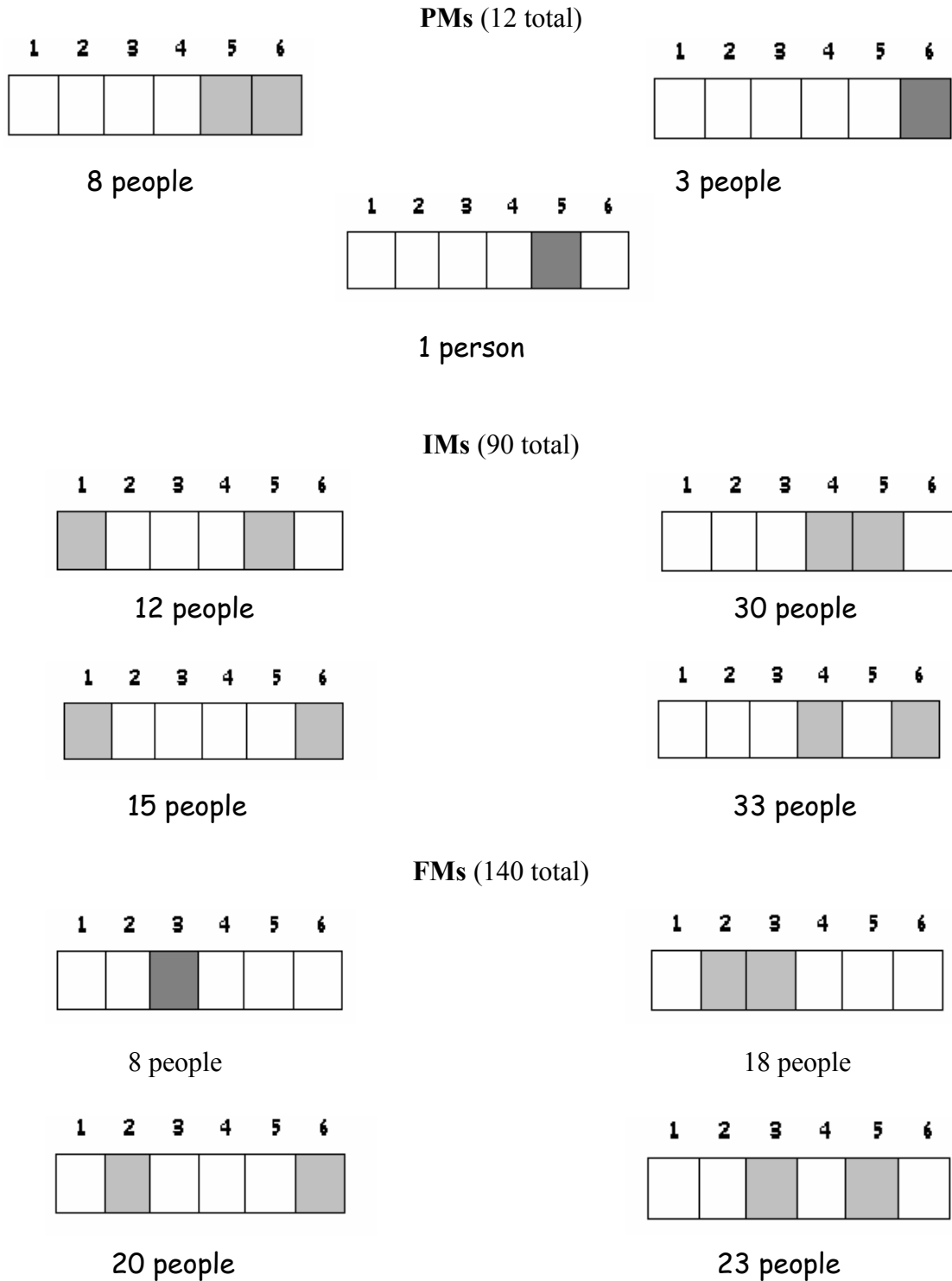
4/5 genotype

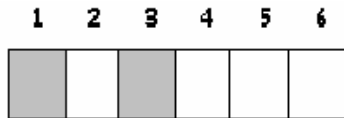


2/2 genotype

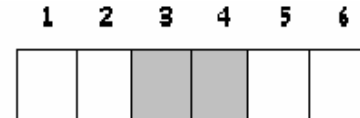
Results:

Here are the results. They are grouped by metabolizer level, showing which alleles were contained by the people in that group.

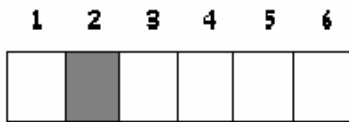




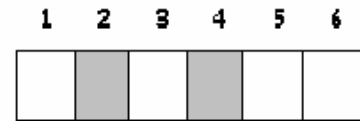
28 people



22 people



7 people



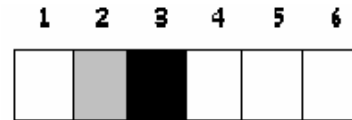
16 people

UMs (8 total)



4 people

3 people



1 person

Directions:

Your job is to analyze the results and attempt to determine all the possible genotypes and which phenotype they connect to. Be careful and make sure to look at all possibilities. Then, form a hypothesis about the causes of differing metabolism levels. That is, try to categorize what type of genotypes (allele combinations) lead to which of the four types of metabolizers. For example, having two reduced activity alleles, such as allele 1 and 4 or 1/4, may lead to a specific ability to metabolize, such as intermediate metabolism (this may or may not be true – you need to study the data!)