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## Drugs and DNA: How Genetics Affect Drug Metabolism

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Drugs and DNA: How Genetics Affect Drug Metabolism  
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Many researchers and clinicians are interested in how a patient's individual genetic makeup could predict the appropriate medication and dose for that patient. The tailoring of prescribing practices to an individual patient has been coined personalized medicine, and incorporating genetic information into the prediction is called pharmacogenetics. One way to predict drug response, or efficacy, is by looking at enzymes within the liver that metabolize, or break down, drugs. Many of these enzymes belong to a class called the Cytochrome P450s (CYPs). Specifically, two closely related enzymes, CYP3A4 and CYP3A5, are involved in metabolizing 50% of drugs currently on the market (eg: statins, antiepileptics, anticancer agents, and antidepressants). Within the genes that code for these enzymes, there are single nucleotide polymorphisms (SNPs), which are single base pair changes in the DNA. SNPs can change the rate of metabolism of drugs, toxins, and compounds found naturally in the body. However, with interest in personalized medicine on the rise, some populations, who experience health disparities or are medically underserved, are not always included in research, and therefore, not benefiting from genetic-guided therapies. We previously completed a study with participants from the Confederated Salish and Kootenai Tribes (CSKT), located on the Flathead Reservation in northwest Montana. Select CYP enzymes were genotyped, including *CYP3A4* and *CYP3A5*. Most SNPs identified in the CSKT participants were found at frequencies similar to those reported in European-descended populations. Interestingly, one specific SNP, called *CYP3A4\*1G*, was discovered at a high allele frequency (26.81% in CSKT compared to 8.3% in Europeans). These allele frequencies mean that approximately 7% of the CSKT population carry two copies of the SNP while approximately 39% carry one copy. The physiological significance of this SNP is unclear as there are limited and confounding data, however, most of the data published to date suggests that the SNP causes decreased metabolism of drugs. Clinically, this could result in a need for a decreased dose of medication. In addition, this *CYP3A4* SNP was observed to be often inherited with another SNP in the related *CYP3A5* gene, called *CYP3A5\*3*, which encodes for a nonfunctional enzyme. These SNPs found in the CSKT are of particular interest, because inheriting these two SNPs together could cause drastic changes in drug metabolism since the two enzymes metabolize many of the same drugs. We propose that the *CYP3A4\*1G* SNP results in a decrease in clearance via drug metabolism of CYP3A4 substrates. We are using human B-lymphocyte cells to assess CYP3A4 enzyme function and total enzyme content. We have selected B-lymphocyte cells from the Coriell Cell Repository that differ only by *CYP3A4* genotype. The *CYP3A4* genotype of the three cell lines are *\*1/\*1* (wild-type), *\*1/\*1G*, and *\*1G/\*1G*. To control for the *CYP3A5* genotype, all cells were selected based on a *\*1/\*1* *CYP3A5* genotype. In addition to B-lymphocyte samples, we will also investigate *CYP3A4\*1G* activity and content in liver microsome samples from the University of Washington School of Pharmacy Liver Bank. The livers have *\*1/\*1*, *\*1/\*1G*, and *\*1G/\*1G* genotypes of *CYP3A4*. However, due to the limited sample of livers, we will not be able to control for *CYP3A5*, and the samples will have variable *CYP3A5* genotypes. To evaluate enzyme function in both the

B-lymphocytes and liver microsomes, we will use a P450-Glo™ Assay. This assay produces light which will be measured by a luminometer. The amount of light emitted is proportional to CYP3A4 enzyme activity. Lymphocyte and microsomal CYP3A4 and CYP3A5 protein content will be measured by Western Blot using specific CYP3A4 and CYP3A5 antibodies. Also, CYP3A4 and CYP3A5 mRNA levels will be quantitated by real time PCR. We expect to find that samples with *CYP3A4\*1G/\*1G* genotypes will have a slower maximum rate of metabolism than cell lines with *CYP3A4\*1/\*1* genotype. This is due to the expectation that *\*1G* carriers will have less CYP3A4 protein content than the wild-type samples. Also, we expect that binding affinity between the enzyme and medications will remain unchanged between genotypes due to the intronic location of the SNP. These findings will be important because they could help guide clinicians in proper treatments for the CSKT population who carry the variant allele. Our goal is to decipher the impact of the *CYP3A4\*1G* SNP and the metabolic consequences of inheriting it with *CYP3A5\*3*.