



Allelic Expression of Phase II Metabolizing Enzymes and Relationship to Irinotecan Toxicity

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Many drugs are associated with variable response rates and, of the 1,200 drugs approved for use in the United States, about 15% are associated with adverse drug responses (Jorde, Carey, & Bamshad, 2010c). Often, variable response and risk for toxicity can be explained because of differences in genes and in the proteins encoded by those genes. Single nucleotide polymorphisms (SNPs) responsible for variable expression can be found in genes encoding for drug targets (receptors) or in genes responsible for drug disposition, including those that encode metabolizing enzymes or transporter molecules (Jorde et al., 2010c; Kuo, Lee, & Ma, 2009; Ma & Lu, 2011). Although pharmacogenetics usually refers to drug interactions based on a relatively small number of genes, pharmacogenomics is the preferred term because it refers to interactions within the entire complement of genes (Krau, 2013; Ma & Lu, 2011). This article discusses how SNPs in phase II metabolizing enzymes can influence irinotecan-induced toxicity.

Metabolism of Drugs

Phase I metabolism is an oxidation-reduction process that, in most cases, converts the active drug into inactive metabolites, discontinuing the action of the drug. This process is, primarily, a function of enzymes from the cytochrome p450 (CYP) system. SNPs encoding *CYP2D6*, *CYP2C9*, and *CYP2C19* are well-studied and have implications for a number of common drugs.

Enzymes responsible for phase II metabolism are conjugating enzymes. They form covalent linkages between the phase I metabolite and endogenous chemical molecules, like hydrogen, sulfate, glucose, or acetate (Correia, 2012). Phase II compounds are generally inactive, and they are highly polar, enabling

the metabolite to be eliminated through the urine or feces. Insufficient production of these enzymes means phase I metabolites circulate longer, putting the drug recipient at greater risk for toxicity.

Genetic Polymorphisms

Every protein made by the body has a “recipe” (gene) at a specific chromosome location, known as the locus. Adenine (A), guanine (G), cytosine (C), and thymine (T) are the nucleotide building-blocks of the DNA double helix, and they are the basic components of each “recipe” in the body. Nucleotide chains can be rearranged (e.g., ACCAAGTGC, CAGCTGGAT) in enough configurations to make the 20,000–25,000 genes found in the human body (Jorde, Carey, & Bamshad, 2010a). Changes in any of these can change the configuration or function of the final gene product, the protein. For example, a single-nucleotide substitution can change GUU (guanine, uridine, uridine), the RNA recipe for valine, to GAU (guanine, adenine, uridine), the RNA recipe for glutamate. This SNP is responsible for the hemoglobin changes associated with sickle cell disease (Jorde, Carey, & Bamshad, 2010b) and is but one of thousands possible in the human genome. Polymorphisms can affect single or multiple nucleotides within the genetic recipe. Mutations in genes encoding phase II metabolizing enzymes can affect an individual’s ability to effectively excrete phase I metabolites.

Uridine Diphosphate Glucuronosyltransferases

Human uridine diphosphate glucuronosyltransferases (UGT) is a superfamily of conjugating metabolizing (phase II) enzymes. UGT catalyzes the transfer of glucuronic acid to the functional group

(hydroxyl, carboxyl, amino, or sulfur) of a drug substrate. This facilitates excretion of the metabolite into the urine or bile by increasing its polarity (Court, 2007; Li & Bluth, 2011; Ma & Lu, 2011). To date, 17 human UGT genes have been identified, and they are classified into two subcategories, UGT1 and UGT2 (Li & Bluth, 2011). Polymorphisms, or genetic variants, have been identified for almost all members of the UGT family, and each can affect the function or expression of the protein.

UGT1A1 is a gene that encodes UGT and is responsible for the conjugation of bilirubin and many drug compounds (Court, 2007; Li & Bluth, 2011; Ma & Lu, 2011). Decreased catalytic activity of UGT puts individuals expressing low-functioning *UGT1A1* variants (alleles) at greater risk for drug toxicity. *UGT1A1*28* and *UGT1A1*6* are two such variants with significance to oncology. Each of these alleles is associated with decreased glucuronidation (inactivation) of SN-38, the active metabolite of irinotecan (Court, 2007; Li & Bluth, 2011; Ma & Lu, 2011). Decreased *UGT1A1* activity means that SN-38 cannot be effectively converted to its β -glucuronide derivative, necessary for its excretion (Li & Bluth, 2011).

The *UGT1A1*28* polymorphism is found in the gene’s promoter region. The promoter region is found immediately upstream of the genetic recipe. RNA polymerase binds to this promoter region on DNA to begin the transcription process (copying RNA from DNA). The transcribed RNA will then be read by the ribosomes to make the protein, in this case UGT. Polymorphisms in the promoter region will not affect the recipe

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