Discovery of Rs887829 as the Genetic Polymorphism Responsible for Reduced UGT1A1 mRNA Expression in a Diverse Cohort

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UGT1A1 is an enzyme involved in metabolizing Irinotecan, a DNA topoisomerase class I inhibitor chemotherapeutic drug. Polymorphisms within the UGT1A1 promoter reduce UGT1A1 mRNA expression, rendering individuals susceptible to heightened drug toxicity. Irinotecan toxicity makes it crucial to identify the polymorphisms responsible for reduced mRNA expression and then use the polymorphism as a biomarker for personalized therapy. Previous research studied only Caucasian individuals and determined that a polymorphism within the UGT1A1 gene promoter's TATA box was responsible for reduced mRNA expression. Although this polymorphism has been used to guide Irinotecan prescriptions, it is loosely associated with reduced mRNA expression in other populations. Comparing drug response rates between Caucasians and African Americans prescribed Irinotecan based on the presence of the TATA box polymorphism, reveals reduced response rates among African Americans. Therefore, this research expands its scope to encompass both African-American and Caucasian populations. This study investigates a nearby single nucleotide polymorphism (SNP), rs887829, located within 300 base pairs of and in linkage disequilibrium with the TATA box polymorphism. Liver samples were collected from both groups, with subsequent extraction of gDNA and mRNA. UGT1A1 mRNA expression was recorded for all samples. The UGT1A1 gene promoter region was amplified, and genomic analysis was conducted to determine the genotype for both polymorphisms in all samples. A linear regression model was used to determine the association between the presence of one of the polymorphisms and reduced UGT1A1 mRNA expression. The rs887829 SNP was determined to more accurately predict reduced UGT1A1 mRNA expression in both groups.

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