AMERICAN PSYCHIATRIC ASSOCIATION
ANNUAL MEETING 2012

HIGH PREVALENCE AND SIGNFICANT PHARMACOKINETIC IMPLICATIONS OF THE *CYP2C19* GAIN-OF-FUNCTION ALLELE **17* IN PSYCHOTROPIC-TREATED PATIENTS

Gualberto Ruaño, M.D., Ph.D.
Krystyna Gorowski, M.T.
Bonnie L. Szarek, R.N.
Richard Seip, Ph.D.
Mohan Kocherla, M.S.
John W. Goethe, M.D.

Objective: To establish the frequency of the *CYP2C19 *17* gain-of-function promoter polymorphism *(-806 C>T, rs12248560, increased transcription)* and determine its combinatorial genotypes with *CYP2C9* and *CYP2D6.* A patient homozygous for **17* is classified as an ultra-rapid metabolizer for the CYP2C19 isoenzyme, and the *CYP2C19 *17* allele has been associated with escitalopram therapeutic failure.

Method: We examined 199 European-American psychiatric patients referred to the Genomas Laboratory of Personalized Health at Hartford Hospital for intolerance or resistance to psychotropics. Their DNA was genotyped to detect 10 alleles in *CYP2C19*, including **17* (AutoGenomics Infinity® assays) and 26 alleles in *CYP2C9* and *CYP2D6* (6 and 20, respectively, Luminex xTag® assays).

Results: The *CYP2C19 *17* allele frequency was 18.6%, consistent with previous reports. Of the 199 patients, 52 were *CYP2C19 *17* heterozygotes, 12 were compound heterozygotes of **17* and null-function alleles, and 5 were homozygotes. The number of patients with non-Reference alleles in *CYP2C19, CYP2C9*, and *CYP2D6* (triple gene alterations) was 20. Of these, 14 patients were *CYP2C19 *17* carriers and 6 were carriers for *CYP2C19* null alleles. Ultra-rapid metabolizer status for isoenzyme CYP2C19 was assigned to the 5 patients who were **17* homozygotes. Of these, 1 patient was an ultra-rapid metabolizer for both *CYP2C19* and *CYP2D6*, which correlated with therapeutic failures to multiple psychotropics. The other 4 *CYP2C19* ultra-rapid metabolizers were deficient or poor metabolizers for *CYP2D6*, resulting in pronounced functional disparity between the CYP2C19 and CYP2D6 isoenzymes, which are the two major routes for psychotropic metabollsm.

Conclusions: The **17* allele significantly increases the polymorphism of *CYP2C19* and contributes to a supra-functional status for the isoenzyme, leading to an ultra-rapid metabolizer status in 3-4% of patients. In combination with *CYP2C9* and *CYP2D6* polymorphisms, the *CYP2C19 *17* more than doubled the prevalence of individuals with triple gene alterations. The pharmacogenetic profile of psychiatric patients is critically enhanced by incorporation of *CYP2C19 *17* in the diagnostic allele panel.

Educational Objectives: At the conclusion of this presentation, participants will be able to *(1)* describe the prevalence and significance of *CYP2C19* loss- and gain-of function drug metabolism alterations, *(2)* assess the utility of CYP450 combinatorial genotyping in characterizing an individual's metabolic phenotype, and *(3)* utilize CYP450 combinatorial genotype values to improve psychotropic management.

Disclosure: Dr. Ruaño, Ms. Gorowski, and Mr. Kocherla are shareholders and/or employees of Genomas, Inc. Dr. Goethe, Dr. Seip, and Ms. Szarek have no disclosures.