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

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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 metabolism.

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.

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