Companion studies offer promise for personalized management of psychotropic therapy

Two pharmacogenetics studies published as companion papers in the August issue of *Biomarkers in Medicine* have demonstrated the clinical implications of a systems approach to CYP450 genotyping and its physiogenomic analysis for the personalized management of psychotropics. Many of the most utilized medications, particularly psychotropics, are metabolized by multiple CYP450 pathways, each of which, in isolation may inadequately account for a drug's pharmacokinetic properties. Distributed substrate affinity would benefit from a combinatorial approach that considers CYP2C9, CYP2C19 and CYP2D6 as integrative components of a hepatic enzyme system for drug metabolism. The research at Hartford Hospital’s Institute of Living and Genetics Research Center and at the Genomas Laboratory of Personalized Health (Hartford, Connecticut USA) by Gualberto Ruano, M.D., Ph.D., and John Goethe, M.D., points to the value of combinatorial CYP450 genotyping for the analysis of respective genes and isoenzymes as components of a prescription “routing” system for patient-specific selection of psychotropics optimized to the innate drug metabolism reserve of each individual.

In the first article (1), 1199 psychiatric referred patients were genotyped for a total of 30 polymorphisms in the CYP2C9, CYP2C19 and CYP2D6 genes (5, 7, and 18 allelic loci, respectively). There was wide variation and high prevalence of combinatorial alterations in the CYP2C9, CYP2C19 and CYP2D6 genes. Of the 1199 patients genotyped, 7.4% were not polymorphic in any of the 3 genes, 41% were polymorphic in 1 gene, 45% were polymorphic in 2 genes, and 6.6% were polymorphic in all 3 genes. Greater than 50% of the population carried polymorphisms in either 2 or all of the CYP2C9, CYP2C19 and CYP2D6 genes. Novel drug metabolism indices from the combinatorial genotyping data were developed (metabolism reserve, metabolism alteration, allele alteration, gene alteration) and scored for each patient, creating distributions and rankings of innate drug metabolism capacity to which individuals could be benchmarked.

In the second article (2), associations between CYP2C9, CYP2C19 and CYP2D6 combinatorial genotypes and dyslipidemia in 150 psychiatric hospitalized patients with a diagnosis of Major Depressive Disorder treated with psychotropic medications (98% received antidepressants, and 65%, antipsychotics) were established. Physiogenomic methods were used to quantify the genotypes according to CYP450 combinatorial and drug-specific metabolism indices. The multi-gene physiogenomic analysis revealed significant correlations among all 4 combinatorial indices and dyslipidemia measures (LDLc, HDLc, LDLc/HDLc ratio). Patients with a greater drug metabolism reserve evidenced lower LDLc, lower LDLc/HDLc ratio, and higher HDLc values. Conversely, patients with a greater number of alterations affecting drug metabolism evidenced higher LDLc, higher LDLc/HDLc ratio, and lower HDLc. Patients with the least metabolic reserve index and greatest alteration indexes were found to have the most marked dyslipidemia.

Gualberto Ruano, M.D., Ph.D., Director of Genetics Research, Hartford Hospital, and President of Genomas stated: "CYP450 combinatorial indices for innate drug metabolism function may be superior in accuracy and utility to phenotype descriptors of metabolizer status (e.g. poor, intermediate, extensive, ultra-rapid) due to the resolution and scope of this approach. The combinatorial index ranking curves are useful in benchmarking innate drug metabolism reserve and identifying patients at the extremes of metabolic capacity to correlate with clinical outcomes. Our results show that combinatorial CYP450 genotyping and corresponding quantitative indices of pharmacogenetic functional status have potential clinical utility in psychiatry for evaluating the risk of iatrogenic cardiometabolic effects of psychotropic treatment."

Harold I. Schwartz, M.D., Psychiatrist-in-Chief and Vice President, Behavioral Health, Institute of Living at Hartford Hospital observed: "These findings support a public health imperative for the wide use of DNA typing to
manage psychotropics. It is rare that truly novel, unconventional approaches to matters believed to be understood scientifically, can be revisited, recast, and in the process, transformed into clinically effective knowledge. The companion papers document such an accomplishment, the fruition of 6 years of collaborative clinical research at the Institute of Living and Genetics Research Center of Hartford Hospital.”

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REFERENCES

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ABOUT THE GENETICS RESEARCH CENTER AT HARTFORD HOSPITAL
The Genetics Research Center (GRC) was established in 2004 to advance Personalized Medicine and engage the resources of the Hartford Healthcare System in the development and application of DNA-guided healthcare. The GRC has served as incubator for the biomedical company Genomas Inc. and for its Laboratory of Personalized Health, The GRC genomic database and bio-bank includes over 7000 patients in diabetes, heart disease and mental illness. GRC operates on the philosophy: Research begins with the patient and ends with the patient. Contrasted to clinical trials or animal experiments, GRC pursues clinical practice as a model system for genomic analysis and elevates it to a laboratory for mechanistic inference, a counterpart to animal, cellular, and molecular models of disease. With clinical practice as a model system, GRC accelerates the translation of research findings to personalized healthcare. The expected benefits are the understanding of the physiological and genetic mechanisms underlying disease and development of decision support systems for personalized health care.

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