Catechol O-Methyltransferase Pharmacogenomics: Challenges, and Opportunities

Ming-Fen Ho, Ph.D **Richard M. Weinshilboum, M.D.**

Division of Clinical Pharmacology, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, Minnesota

INTRODUCTION

Catechol O-methyltransferase (COMT) is an example of a genetically polymorphic drug and neurotransmitter metabolizing enzyme that can contribute to both pharmacokinetic and pharmacodynamic variation. However, even though thousands of *COMT* pharmacogenomic studies and many statistically significant effects have been reported, its clinical utility remains unclear. COMT may be an example of a pharmacogene that could have the greatest clinical utility when included in algorithms that integrate the effects of multiple genes and multiple data types.

Catechol O-methyltransferase (COMT) pharmacogenomics represents one of the earliest examples of the use of genetics-genomics in an attempt to understand and predict individual variation in both drug response and neurotransmitter function. COMT was discovered and characterized in 1958 at the U.S. National Institutes of Health in the laboratory of Julius Axelrod (1), an amazingly creative scientist and scientific mentor. That discovery occurred as a result of a systematic search for enzymes that might play a role in catecholamine neurotransmitter function analogous to the role of acetylcholinesterase in cholinergic neurotransmission. However, Axelrod and his coworkers subsequently found that the primary role in the termination of biogenic amine neurotransmission was played by the neural reuptake of biogenic amines mediated by membrane transporters—a discovery for which he shared the 1970 Nobel Prize in Physiology or Medicine.

Genetic variation in the expression of COMT, a drug and neurotransmitter methyltransferase enzyme, was first reported in the mid-1970s (2), well before genes could easily be cloned and characterized, feats that were finally accomplished for the *COMT* gene and its polymorphisms nearly two decades after the first report of its common genetic variation (3), The high and sustained level of interest in *COMT* genomics and pharmacogenomics is demonstrated by the fact that a recent PubMed search for *"COMT* genetic polymorphisms" listed over 2,200 individual publications. However, in spite of that high level of interest, the *Clinical Pharmacology and Therapeutics* invitation to submit originally suggested that the

Corresponding author: Richard M. Weinshilboum, M.D., weinshilboum.richard@mayo.edu, Mayo Clinic 200 First Street SW, Rochester, MN 55905, Phone: +1 507-284-2790.

title of this "Commentary" might be "Waste or Value: COMT Pharmacogenomic Testing", a suggestion that may reflect, at least in part, frustration with the lack of a clear and compelling demonstration of the clinical utility of *COMT* pharmacogenomics. As a result, we felt that it might be helpful to use COMT as a "case study" of the half century of evolution in our understanding of one of the earliest examples of pharmacogenomics to highlight the challenges that we face even as new opportunities in pharmacogenomics are appearing.

The techniques used to first demonstrate genetic variation in human COMT enzyme activity, like those of virtually all human pharmacogenetic studies of that era, were the same as those used by Mendel to study the genetics of peas in his monastery in Brno, ie., they involved studies of the segregation of the trait of interest in families, in this case the segregation of level of COMT enzyme activity. The observation that COMT activity could be measured in red blood cells (RBCs), an easily obtained human tissue, made it possible to conduct large family studies of RBC COMT enzyme activity (2). Those studies demonstrated that level of COMT enzyme activity was inherited as a monogenic trait with a trimodal frequency distribution compatible with a variant allele for low enzyme activity with a minor allele frequency (MAF) of nearly 50% in European populations. Subsequent molecular genomic studies showed that these observations resulted from a non-synonymous (ns) single nucleotide polymorphism (SIMP), rs4680, that resulted in the encoded amino acid being either methionine or valine (3). This series of genetic and molecular genetic observations from decades ago raised hopes for rapid progress in the clinical application of COMT pharmacogenomics to help individualize therapy with catechol drugs like L-DOPA and methyldopa—both of which are excellent COMT substrates—as well as possible insight into the pathophysiology and treatment of neuropsychiatric disease such as major depressive disorder.

Now, over four decades later, we understand that those initial hopes were overly optimistic. That is true in part because of the structural complexity of the *COMT* gene, as described subsequently. Additional complexity results from the fact that COMT is a drug metabolizing enzyme, so it can influence the pharmacokinetics (PK) of drugs that are catechol substrates but it also has a role in complex neurotransmitter function, so it can also influences pharmacodynamics (PD). In addition, the gene is much more complex than was initially appreciated since it is now known to have two major sites of transcription initiation. Transcription of mRNA encoding a cytosolic form of the enzyme—the most common form expressed in peripheral organs such as liver and kidney—is driven by a "proximal" promoter located in intron 2 of the gene, while transcription of mRNA encoding a membrane bound isoform that is highly expressed in the brain is initiated 20 kb upstream at a "distal" promoter. To complicate the situation further, translation initiation for the membrane bound form of the enzyme begins 50 codons 5' of the translation initiation ATG for the soluble cytosolic isoform (4). The cytosolic and membrane bound isoforms display differences in their ratios across tissues as well as differences in substrate affinities between the cytosolic and the membrane bound isoforms. The SNP most commonly genotyped in clinical pharmacogenomic studies, (rs4680), alters the encoded amino acid at codon 108/158 in the soluble/membrane bound isoforms, respectively. However, even that degree of molecular complexity represents an over-simplification since the GTEx database(http://gtexportal.org/

home) now lists 11 different COMT transcripts that encode proteins of 6 different lengths. The functional importance and implications of this degree of molecular complexity is not yet fully understood.

It is against this molecular background that the results of clinical studies of COMT pharmacogenomics must be evaluated. Of the over 2,200 publications on the topic of *"COMT* genetic polymorphisms" mentioned previously, the vast majority studied possible PK associations of the codon 108/158 polymorphism with variation in blood drug levels or drug response for COMT substrates like L-DOPA in patients with Parkinson's disease or methyldopa in hypertensive patients. On the PD side, there have been numerous reports of the association of *COMT* genotypes for the codon 108/158 SNP with response to antidepressant and antipsychotic drugs and—especially— response to the drug therapy of pain with opioids. In the latter situation, *COMT* is most often only one of a group of genes that are studied, a group that almost always includes polymorphisms in the mu opioid receptor gene *OPRM1* and the opioid transporter gene *ABCB1*. Finally, *COMT* polymorphisms have also been associated with disease risk. For example, in a set of unexpected observations, SNPs in the "distal promoter" of the *COMT* gene have been reported to be associated with risk for breast cancer in premenopausal women—results that have been speculated to be due to a role for catechol estrogens in risk for breast cancer and the methylation of those compounds by COMT. A rapid survey of these numerous studies also shows that many additional *COMT* SNPs beyond rs4680 have been genotyped in clinical studies and that "panels" of additional polymorphic genes—depending on the phenotype of interest—are increasingly being genotyped together with *COMT* (eg. *OPRM1* and *ABCB1* in studies of opioid response). However, when the "customer information" supplied by three different clinical pharmacogenomic laboratories was compared, the indications for obtaining *COMT* genotype information differed substantially among the three laboratories. It is this mix of statistically significant clinical associations with confusion with regard to exactly what information to provide to clinicians and how to do so in a readily understood format, ideally at the point of care, that makes *"COMT* Pharmacogenomics" a representative "case study" for the status of much of pharmacogenomics in 2019. Obviously, whether we are discussing *COMT* or other pharmacogenes, medical institutions must invest in the infrastructure required to bring pharmacogenomic information to healthcare professionals at the point of care in an easily understood and readily usable form. .

As we look to the future, it should no longer be necessary to make the point that genomics can influence drug response phenotypes—that is clear. However, the way(s) in which we provide accurate patient-specific pharmacogenomic information to physicians will have to evolve. One possible approach might involve integrating both PK and PD SNPs—perhaps including other "omics" data--within algorithms developed using machine learning and artificial intelligence capable of providing validated treatment recommendations to the physician—not just genotypes or phenotypes derived from genotypes. Initial steps toward that goal are already being taken. For example, an algorithm doing just that for the selective serotonin reuptake inhibitors (SSRIs) that are used to treat depression has recently been developed. That algorithm—replicated in a series of SSRI clinical trials-increased the predictive accuracy for SSRI response from 55–60% using clinical data alone to 70–85%, a

value with clinical utility. An initial publication on the underlying analytical methods used to develop the SSRI response algorithm was published in the IEEE computer science journal "Computational Intelligence" and was highlighted graphically on the cover of that journal (see Figure 1) (5). This type of approach may represent one facet of the future for *COMT* pharmacogenomics, so it seems appropriate to end this "Commentary" on COMT, which began in 1958 with Julius Axelrod, with efforts to predict treatment outcomes for the SSRIs that were made possible by his Nobel Prize research.

FUNDING

REFERENCES

(1). Axelrod J & Tomchick R Enzymatic O-Methylation of Epinephrine and Other Catechols. Journal of Biological Chemistry 233, 702–5 (1958). [PubMed: 13575440]

(2). Weinshilboum RM & Raymond FA Inheritance of low erythrocyte catechol-o-methyltransferase activity in man. American journal of human genetics 29, 125–35 (1977). [PubMed: 848488]

(3). Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL & Weinshilboum RM Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 6, 243–50 (1996). [PubMed: 8807664]

(4). Tenhunen J, Salminen M, Lundstrom K, Kiviluoto T, Savolainen R & Ulmanen I Genomic organization of the human catechol O-methyltransferase gene and its expression from two distinct promoters. European Journal of Biochemistry 223,1049–59 (1994). [PubMed: 8055944]

(5). Athreya A et al. Augmentation of Physician Assessments with Multi-Omics Enhances Predictability of Drug Response: A Case Study of Major Depressive Disorder. IEEE Computational Intelligence Magazine 13, 20–31 (2018). [PubMed: 30467458]

Figure 1.
The Figure shows the cover of the August 2018 edition of "IEEE Computational Intelligence" graphically highlighting an article in that publication describing methods by which artificial intelligence had been used to create a predictive algorithm for SSRI response in patients with Major Depressive Disorder. © 2018 IEEE. Reprinted, with permission, from IEEE Computational Intelligence Society (IEEE/CIS).