Abstract: Genetic polymorphisms and environmental factors work with and against each other to affect neurodevelopment and the delicate balance of neurotransmitters that underlie psychiatric disorders. This article explores the complex nature of gene-gene and gene-environment interactions and the implications for diagnosis and treatment of disease. As an example of this dynamic relationship, the gene for catechol-O-methyltransferase (COMT, a dopamine-degrading enzyme) and how COMT acts together with other genetic and environmental susceptibility factors to affect cognition and psychiatric disease are discussed.

COMTemplating the Future of Psychiatric Medicine

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Issue
Recent studies have investigated the relationship among polymorphisms in catechol-O-methyltransferase (COMT) and several psychiatric disorders; however, a clearly defined disease risk associated with COMT has yet to be found.

Action
This article reviews the putative relationship of COMT, cognition, and psychiatric disease, with specific emphasis on the synergistic relationship of COMT and methylenetetrahydrofolate reductase (MTHFR) polymorphisms.

Benefit
Given that the future of psychiatric medicine undoubtedly includes an emphasis on gene-based personalized medicine, it is essential to understand how genes and environmental factors can interact to affect the onset, course, and treatment of psychiatric disorders.

Dopamine Homeostasis Is Mediated by COMT in the DLPFC
The dorsolateral prefrontal cortex (DLPFC) is a brain region involved in executive functioning, including working memory. The actions of the DLPFC are mediated—to a certain extent—by dopamine (DA), and it is believed that the cognitive dysfunction evident in many disorders, including schizophrenia, may be partially ascribed to dopaminergic imbalance in the DLPFC. In fact, some have postulated that the relationship between DA in the DLPFC and cognitive function is best described as an inverted “U,” with either too much or too little DA leading to cognitive impairment (Figure 1). 1-3

Figure 1. Dopamine Homeostasis
The relationship between the concentration of DA in the DLPFC and cognition is believed to follow an inverted “U” shape, whereby either too little dopamine (hypodopaminergia) or too much dopamine (hyperdopaminergia) results in cognitive dysfunction. Note that there is a range of dopamine concentrations during which cognitive function would be expected to be normal.
Dopamine homeostasis, the balance between the production and elimination of DA from the synapse, depends primarily on catechol-O-methyltransferase (COMT) in the DLPFC. COMT is an S-adenosylmethionine (SAMe)-dependent methyltransferase enzyme that is responsible for the breakdown of catecholamines such as DA and norepinephrine (NE). A single nucleotide polymorphism (SNP) resulting in the substitution of valine for methionine at codon 158 has been discovered in the COMT gene. The "Val" allele results in a COMT enzyme that is 40% more active than the "Met" allele. Individuals who are homozygous for (have 2 copies of) the Val allele (Val/Val) are thus expected to have decreased DA concentration in the DLPFC compared with Met homozygotes (Met/Met). Heterozygotes (carrying 1 Val and 1 Met allele; Val/Met) have COMT enzyme activity that is somewhere in the middle of the Val/Val and Met/Met homozygotes.

Not surprisingly, COMT genotype predicts performance on working memory tasks that involve the DLPFC. Several studies have found that the Met allele is associated with enhanced working memory, whereas the Val allele is linked with a decreased ability to maintain information. These data have been confirmed with imaging studies that utilize fMRI and show impairment in brain activation in Val-carrying individuals. There have also been numerous association and linkage studies investigating the involvement of COMT genotype with cognitive function in psychiatric disorders; most of these studies focus on COMT as a risk factor for schizophrenia.

COMT and Psychiatric Disorders

Despite the plethora of research looking at the putative relationship between COMT genotype and schizophrenia, no consensus has been reached: Many studies indicate the Val allele as a susceptibility factor for schizophrenia, but other studies have failed to find such a connection. Contrary results have also been published concerning the relationship of COMT genotype with other psychiatric conditions, including attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), bipolar disorder, and depression.

The fact that there appears to be no cut-and-dry relationship between COMT genotype and any psychiatric disorder is not surprising; in fact, the blurriness of the relationship is what can be expected in this new age of personalized medicine and pharmacogenetics. At the level of the individual, COMT is but one piece of a vast and intricate puzzle. However, we are rapidly finding more puzzle pieces and establishing how the pieces interact to bring about the particular molecular and cellular characteristics that underlie behavior. In this context, COMT would be expected to function on a background of other genetic polymorphisms and environmental factors that affect DA levels in the DLPFC (Figure 2). For example, COMT has been found to have a synergistic epistatic interaction with other candidate susceptibility genes for schizophrenia and cognitive dysfunction, including neuregulin-1 (NRG1) and the Type II glutamate receptor 3 (GRM3). COMT also shares an interesting relationship with another putative susceptibility gene for schizophrenia: methylenetetrahydrofolate reductase (MTHFR) (Figure 3). MTHFR is involved in the metabolism of dietary folate and, ultimately, in the production of SAMe, the major methyl donor in the brain. COMT, as a methyltransferase, gets its methyl group from SAMe. Additionally, the methyl groups supplied by SAMe are used in the methylation of the COMT promoter. Two separate polymorphisms in MTHFR (known as the T allele and C allele) result in altered MTHFR activity. Depending on the particular variant of MTHFR present, there will be more or less methylation of the COMT promoter, with increased COMT promoter methylation leading to reduced COMT expression. This interaction may be beneficial or detrimental to DA homeostasis, depending on the COMT genotype.

![Figure 2. The Balance Between Genetic Susceptibility and Disease Presentation](image)

Dopamine concentration in the dorsolateral prefrontal cortex (DLPFC) is affected by many factors, including genetic makeup and environmental factors. Each genetic polymorphism and environmental factor that increases susceptibility to a psychiatric disease can be thought of as an additional weight that tips DA homeostasis toward imbalance. (A) A normal balance of DA reflects the notion that any detrimental genetic polymorphism that may lend susceptibility to a psychiatric disorder is counterbalanced by other genetic polymorphisms and environmental factors. For example, an individual may have the COMT Val allele, which predisposes him or her to schizophrenia by leading to reduced DA levels in the DLPFC; however, in the absence of genetic polymorphisms that may further reduce DA levels and a lack of detrimental environmental factors, the individual will likely function normally. (B) A slight imbalance in DA concentration may result from having polymorphisms in several genes that predispose an individual to a psychiatric disorder (e.g., both the COMT Val allele and mutated neuregulin-1 gene); however, in the absence of detrimental environmental stimuli or additional predisposing genetic polymorphisms, DA levels may be maintained above the threshold for development of a psychiatric disorder. Interestingly, this individual may display some behaviors (such as increased anxiety) that are characteristic of a psychiatric disorder but do not reach diagnostic criteria. (C) In the presence of multiple genetic polymorphisms, each increasing predisposition to a psychiatric disorder, in addition to environmental factors that further increase disease susceptibility (such as child abuse, smoking, and nutritional deficits), the threshold DA concentration will be breached, leading to presentation of a psychiatric disorder. As DA is not the only neurotransmitter involved in most psychiatric disorders, it should be noted that the accumulation of genetic and environmental factors that affect DA levels may more subtly alter the disease course, presentation, and/or treatment response rather than being the sole determinant of disease onset.
Figure 3. MTHFR and COMT
Polymorphisms in methylenetetrahydrofolate reductase (MTHFR) and catechol-O-methyltransferase (COMT), as well as environmental factors, act synergistically to affect dopamine (DA) concentration. (A) When dietary folate levels are adequate and MTHFR polymorphisms are absent, the methyl (CH$_3$) donor S-adenosylmethionine (SAMe) is produced, leading to methylation (silencing) of the COMT gene promoter. Despite the presence of a COMT Val genotype, the excessively active enzyme is not expressed, and DA in the dorsolateral prefrontal cortex (DLPFC) is not markedly metabolized, leaving plenty of DA available to mediate cognitive function. (B) A polymorphism in MTHFR leads to reduced production of SAMe and subsequent expression of COMT. The COMT Val enzyme is then available to break down DA in the DLPFC; however, despite the presence of both MTHFR and COMT polymorphisms leading to reduced available DA in the DLPFC, there may be enough DA present to maintain cognitive function within normal parameters. (C) Mutated MTHFR and COMT, in the presence of detrimental environmental factors (such as reduced dietary folate) or additional polymorphisms in other susceptibility genes, would lead to even less SAMe production and possible pathologic hypodopaminergia in the DLPFC. This accumulation of genetic and environmental risk factors affecting DA production ultimately determines an individual’s behavior and psychiatric condition. (Hcy: homocysteine)

The above examples outline just a fraction of the genes with which COMT likely has epistatic relationships. Thus, it is unlikely that COMT—or any other solitary gene—will single-handedly determine whether one develops a psychiatric disorder. Not only does each individual have a unique combination of genetic polymorphisms that may increase or decrease his or her susceptibility to developing a psychiatric disorder, each individual also has a unique blend of environmental factors that may have epigenetic effects on gene expression or metabolic effects on protein synthesis and degradation. Therefore, even if an individual has the genetic predisposition for developing a psychiatric illness (e.g., schizophrenia), disease symptoms may not manifest unless environmental factors such as dietary deficiencies or marijuana use are present. $^{16}$

The Bottom Line
The future of psychiatric medicine lies within a dynamic context of epistatic relationships, epigenetics, and environment. Both diagnostic techniques and prescribing practices will likely be influenced by the plethora of genetic information that continues to become available. As we learn more about the genetic and environmental factors that establish susceptibility to psychiatric disorders, influence disease presentation and course, and affect treatment response, we will be poised to better diagnose and treat each patient.

References