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Catechol-O-Methyltransferase and Genetic Variation Under Hemizygosity

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Less than a decade after Julius Axelrod initially described catechol *O*-methyltransferase (COMT) (1), an enzyme he had isolated from rat liver to elaborate epinephrine metabolism, Angelo DiGeorge first hinted at a congenital clinical syndrome of hypoparathyroidism and absence of the thymus (2). There is no reason to suspect that these contemporaries, ensconced in entirely different fields and approaches, would have made particular note of each other's work, much less anticipated that their respective discoveries might inextricably converge half a century later in the modern era of psychiatric genetics. More than a translational science parable, the narrative of COMT and its diverse genetically driven perturbations, including hemizygosity in 22q11.2 deletion (DiGeorge/Velo-Cardio Facial [VCFS]) syndromes, is evidence that the phenotypic complexity of neuropsychiatric illness can be recapitulated even at the genetic level.

After its promethean introduction, COMT was shown to be expressed in the brain, where it has the capacity to *O*-methylate neuroactive catechols and is now particularly known for its contributions to intrasynaptic dopamine regulation in tissues with low concentrations of competing dopamine transporter, such as the prefrontal cortex. The *COMT* gene resides at 22q11.2, where its hemizygous deletion along with that of a handful of neighboring genes constitute a rare structural variant (VCFS) strongly associated with neuropsychiatric illness, notably including schizophrenia. *COMT* also contains multiple functional common single nucleotide polymorphisms (SNPs), the most studied of which has been the nonsynonymous coding rs4680, which affects enzymatic activity via altered thermostability of the COMT protein (3). Coincident with the growth of support for dopamine- and prefrontal-dysfunction hypotheses of schizophrenia, the early accumulation of data establishing the neural sequelae of this SNP garnered understandable enthusiasm and has since been followed by multiple studies demonstrating its impact on prefrontal physiology (3-5).

Yet, as well-poised as COMT is as a candidate risk molecule for neuropsychiatric illness and in particular for schizophrenia, its history in common variant (i.e., SNPs) illness risk-association studies has been plainly checkered. As a result, the COMT story has become an

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oft-referenced emblem of key divides in the recent history of psychiatric genetics: hypothesis-driven (i.e., candidate gene study) versus data-driven (i.e., genome-wide association study) approaches; and common/small-effect versus rare/large-effect search strategies (6). This represents a notable irony for a gene that has been unifying in recruiting vigorous study from both basic and clinical scientists, spawning experiments across diagnostic boundaries—in part due to its remarkable pleiotropy (4)—and belonging to the 22q11.2 deletion syndrome whose phenotypic expression and clinical management, like its history, are multidisciplinary affairs. Nonetheless, the apparent conflict between biological plausibility and statistical association with illness that exists for common but not rare *COMT* genetic variation raises critical questions in the era of the increasingly larger, better powered schizophrenia genome-wide association study. Is there still a reasonable case to be made for contributions of common *COMT* variation to schizophrenia? If so, under what conditions?

The new findings of Gothelf *et al.* (7), identifying messenger RNA expression, protein function, and clinical effects of SNPs in the remaining *COMT* allele in 22q11.2 deletion syndrome, take a step toward answering these questions. By cross-leveraging both multiple common/small effect size and rare/large-effect size variation, the work accomplishes a significant elaboration of *COMT* biology, demonstrating complex, multi-locus interactions at the cellular level and addressing the important conundrum of incomplete penetrance in VCFS.

For instance, the study reveals that, among VCFS individuals, not the well-studied rs4680 SNP alone but rather haplotypes including rs4680 best predict *COMT* activity. The importance of multi-marker assays for understanding genetically driven differences in *COMT* function has been shown in previous molecular experiments (8) and underscores the likelihood that one-variant-at-a-time methodologies will miss important genotype-phenotype associations. Here, the question for future experimentation will be how the picture is complicated in the non-VCFS (non-hemizygous) setting.

An additional achievement of this study was the identification of a SNP associated with psychosis and cognitive impairment risk among VCFS individuals. The convergence of associations of both psychotic and cognitive phenotypes with this particular SNP might speak to correlations between these dependent variables in VCFS but is particularly interesting, given recent evidence for an enrichment of SNPs associated with diminished cognitive aptitude in schizophrenia (9), and forwards the possibility that, in the context of VCFS, functional common variation in *COMT* might be an important predictor of neuropsychiatric outcomes. However, as noted by Gothelf *et al.*, (7) their data suggest that the molecular impact of the implicated SNP requires further study to clarify its mechanism of action. For example, the distinguishing effect of this SNP was in the expression of an extended alternate transcript, and its prediction of enzymatic activity was dependent on the status of other *COMT* markers that were not associated with the clinical variables. If the peripheral assays in this study are faithful proxies for central *COMT* function, how might this extended transcript play a role in clinical outcome in a manner that is not simply via gross *COMT* enzymatic activity? Future efforts to elucidate any meaningful differences in the cellular trafficking of this transcript, as suggested by the authors, or perhaps just as

importantly, in the regional expression of this transcript in the brain will be needed to address this quandary.

Further and fascinating support for the notion that individual differences in the regulation of COMT activity and expression derive from a coalescence of multiple *COMT* variants comes from post hoc sequencing analysis in this same report. This led to the identification of an infrequent SNP associated with exceptionally low enzymatic activity and selectively negligible soluble-form catechol-*O*-methyltransferase (S-COMT) protein. A fresh reminder that the library of published data of putative functional single nucleotide polymorphisms (even for an incredibly well-studied gene) is a woefully incomplete repository, this novel discovery asks its own questions: what is the consequence of having no S-COMT? The authors note that the two VCFS study participants carrying the mutation had non-schizophrenia psychiatric diagnoses, but understanding what specific phenotype, if any, this mutation confers will require further investigation. Because S-COMT is expressed at far lower concentrations than membrane-bound COMT in the brain (3), it is likely that any central nervous system effect would be subtle, relative to effects in peripheral tissues, where S-COMT predominates. Nonetheless, for individuals in the general population who are heterozygous for this polymorphism, presumptively, S-COMT levels and activity might mimic that in VCFS. What 22q11.2 deletion syndrome phenotype, if any, would these individuals reiterate? In answering this question, dedicated clinical and multimodal biological screening of the mutation carriers relative to noncarriers would potentially provide specific knowledge of at least one piece of the clearly complex VCFS-COMT puzzle.

Taken together, these results call to consideration the systems level response to subtle genetic modifications in the background of hemizyosity. Might COMT operating at half-speed open a unique molecular window of neuropsychiatric vulnerability, distinct from that existing in the non-22q11.2 deletion syndrome population? Examples of nonlinear biological systems, particularly in the prefrontal cortex where COMT is hypothesized to exert potent effects on cognitive processing (10), abound in the brain, and it is not a foregone conclusion that the same factors that might contribute to impairment in a particular higher-order cognitive function (e.g., working memory or reality testing) under hamstrung catechol catabolism are identical to those that do so under more heterogeneous genetic contexts. This important and empirically testable consideration ultimately will determine how to most thoughtfully apply 22q11.2 deletion findings to more general models of schizophrenia.

In conclusion, if it is possible that a disparate family of *COMT* genetic variants might contribute in concert to COMT expression, activity, and risk of psychosis in VCFS, then the biology of the common variation of this gene likely still has something to say about schizophrenia, although how generalizable this will be to unselected schizophrenia must await future work. If common variation in *COMT* lends psychosis risk only in a particular neurogenetic context (such as but perhaps not limited to VCFS), it is understandable why statistical support for *COMT* from past association studies in broader schizophrenia populations could be weak: either the necessary context is specific to VCFS or the necessary context can occur in non-VCFS individuals, but canonical linear univariate analyses (that do not consider multi-locus interactions) are not sensitive to the interaction. Perhaps most

instructive, by opening a new and dynamic chapter in the COMT narrative, the multi-faceted approach of Gothelf *et al.* highlights the potential of translational research on neuropsychiatric outcomes in copy number variant conditions to identify novel risk biology and ultimately therapeutic targets that might otherwise have been neglected.

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References

1. Axelrod J. O-methylation of epinephrine and other catechols in vitro and in vivo. *Science*. 1957; 126:400–401. [PubMed: 13467217]
2. Cooper MD, Peterson RDA, Good RA. A new concept of the cellular basis of immunity. *The Journal of Pediatrics*. 1965; 67:907–908.
3. Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am J Hum Genet*. 2004; 75:807–821. [PubMed: 15457404]
4. Mier D, Kirsch P, Meyer-Lindenberg A. Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. *Mol Psychiatry*. 2010; 15:918–927. [PubMed: 19417742]
5. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Natl Acad Sci U S A*. 2001; 98:6917–6922.
6. Collins AL, Kim Y, Sklar P, O'Donovan MC, Sullivan PF. Hypothesis-driven candidate genes for schizophrenia compared to genome-wide association results. *Psychol Med*. 2012; 42:607–616. [PubMed: 21854684]
7. Gothelf D, Law AJ, Frisch A, Chen J, Zarchi O, Michaelovsky E, et al. Biological effects of *COMT* haplotypes and psychosis risk in 22q11.2 deletion syndrome. *Biol Psychiatry*. 2014; 75:406–413. [PubMed: 23992923]
8. Nackley AG, Shabalina SA, Tchivileva IE, Satterfield K, Korchynskyi O, Makarov SS. Human catechol-O-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. *Science*. 2006; 314:1930–1933. [PubMed: 17185601]
9. Lencz T, Knowles E, Davies G, Guha S, Liewald DC, Starr JM, et al. Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: A report from the Cognitive Genomics consortium (COGENT). *Mol Psychiatry*. 2013 [published online ahead of print December 17]. 10.1038/mp.2013.166
10. Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci U S A*. 2003; 100:6186–6191. [PubMed: 12716966]