

## Complex Genetics in Human Brain: Lessons from COMT

Speaker: Daniel R. Weinberger, M.D.  
National Institute of Mental Health, NIH

The principle of Imaging Genetics is to increase the effect size, or the penetrance of genetic variation, by studying a biological phenotype presumably related to the gene's biology. There are two payoffs to Imaging Genetics: 1) having a phenotype that potentially intermediates between gene effects themselves and behavior, and 2) to understand the effects in brain of genetic variation. In applying this principle, Dr. Weinberger picked one gene that has recently emerged as a potential psychiatric gene, the COMT gene. From this experience he has some general lessons to share. The first one is that genes related to psychopathology are *not* about psychiatric diagnoses, *per se*. In other words, the human genome did not evolve with respect to conventional diagnostic classifications. Second, genes related to psychopathology are about the *development* and function of diverse brain circuits related to the processing of cognitive and emotional information. And third, "psychopathology genes" show protean phenotypic associations because their effects vary depending on the biologic context, e.g. on the specific information being processed in these circuits, on the impact of other genes and environmental factors, and on interactions with age, which also targets the same circuits. Neuroanatomical and pharmacological studies in both animals and humans have shown that catechol-O-methyltransferase (COMT), the enzyme that principally breaks down dopamine, is abundant in the cerebral cortex and is functionally related with prefrontal executive functions such as working memory. In terms of genetics, there is a functional polymorphism in the COMT gene that markedly affects enzyme activity and that appears to uniquely impact prefrontal dopamine (commonly known as the "COMT val158/108met polymorphism"). Imaging data has shown that COMT genotype predicts performance on prefrontal executive cognition, emotion (via hippocampal processing) and reward (via midbrain DA metabolism). Despite the weak penetrance of COMT variation seen in "classic" haplotype studies of schizophrenic subjects, the robustness of the penetration of COMT variation in brain function gives neural basis for the association of behavioral traits and COMT. Dr. Weinberger recently found an association between schizophrenia and "inefficient" COMT diplotypes in a case-control study done in 297 schizophrenics otherwise negative for the classic COMT haplotype. This evidence supports the fact that the nonlinear, combinatorial interplay of alleles at multiple loci within the gene may be a playing factor, at least for this gene, on which there has been an evolutionary compensation for the val/met effect. Other reasons for the weak penetrance of COMT are the role of possible interactions with other genes (such as GRM3 in Schizophrenia), and the role of environmental factors including age or teenage marijuana use. In conclusion, **there is no good or bad COMT allele or haplotype, per se. Context is critical.**