

Title: COMT val¹⁵⁸met genotype polymorphism and cognitive performance in Parkinson's disease with and without selegiline treatment.

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Abstract: This project will investigate the influence of 3 common polymorphisms within the catechol-O-methyltransferase (COMT) gene and their impact on results of neuropsychological testing in Parkinson's disease (PD) subjects. Specifically, DNA specimens (collected from 452 of participants diagnosed as having PD in the DATATOP study) will be genotyped to determine to characterize codon 158 for allelic substitutions of valine for methionine. This amino acid change increases the thermostability of COMT, thereby enhancing its enzymatic activity in catecholamine catabolism. Our study proposal follows from other research that has discerned a major influence of this COMT gene polymorphism on cognition in PD and other conditions. We hypothesize that increasing the loading of *val* alleles (e.g., genotypes with *val-met* and *val-val* genotype) will be associated with improved performance on neuropsychological testing requiring components of executive function. Furthermore, we expect that other functions involving the maintenance of information in working memory is expected to show improvement related to *met*-containing genotypes. The neuropsychological testing battery used in the DATATOP study permits these questions to be explored in a large number of non-demented and unmedicated PD subjects. In addition to evaluating the genotype effects on initial cognitive testing, we will investigate changes developing over the 2 years of the study (for those subjects who did not receive active medication). For those subjects who did receive the monoamine oxidase-B (MAO-B) inhibitor selegiline (deprenyl), their performance will be compared before and after the start of this medication.