

COMT haplotypes suggest P2 promoter region relevance for schizophrenia

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Molecular Psychiatry (2004) 9, 859–870. doi:10.1038/sj.mp.4001496

Published online 6 April 2004

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A recent study found, in a large sample of Ashkenazi Jews, a highly significant association between schizophrenia and a particular haplotype of three polymorphic sites in the catechol-O-methyl transferase, COMT, gene: an IVS 1 SNP (dbSNP rs737865), the exon 4 functional SNP (Val158Met, dbSNP rs165688), and a downstream SNP (dbSNP rs165599). Subsequently, this haplotype was shown to be associated with lower levels of COMT cDNA derived from normal cortical brain tissue, most likely due to cis-acting element(s). As a first step toward evaluating whether this haplotype may be relevant to schizophrenia in populations other than Ashkenazi Jews, we have studied this haplotype in 38 populations representing all major regions of the world. Adding to our previous data on four polymorphic sites in the COMT gene, including the Val158Met polymorphism, we have typed the IVS 1 rs737865 and 30 rs615599 sites and also included a novel IVS 1 indel polymorphism, yielding seven-site haplotype frequencies for normal individuals in the 38 globally distributed populations, including a sample of Ashkenazi Jews. We report that the schizophrenia-associated haplotype is significantly heterogeneous in populations worldwide. The three-site, schizophrenia-associated haplotype frequencies range from 0% in South America to 37.1% in Southwest Asia, despite the fact that schizophrenia occurs at roughly equal frequency around the world. Assuming that the published

associations found between the exon 4 Val158Met SNP and schizophrenia are due to linkage disequilibrium, these new haplotype data support the hypothesis of a relevant cis variant linked to the rs737865 site, possibly just upstream in the P2 promoter driving transcription of the predominant form of COMT in the brain. The previously described HindIII restriction site polymorphism, located within the P2 promoter, varies within all populations and may provide essential information in future studies of schizophrenia.

Keywords: COMT; haplotypes; schizophrenia; linkage disequilibrium; functional variation; P2 promoter; population variation