

Genetic variants of the folate metabolic system and mild hyperhomocysteinemia may affect ADHD associated behavioral problems.

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Abstract

An etiologically complex disorder, Attention Deficit Hyperactivity Disorder (ADHD), is often associated with various levels of cognitive deficit. Folate/vitamin B9 is crucial for numerous biochemical pathways including neural stem cell proliferation and differentiation, regulation of gene expression, neurotransmitter synthesis, myelin synthesis and repair, etc. and a scarcity has often been linked to cognitive deficit. Our pilot study in the field revealed significant association of few genetic variants with ADHD. Mild hyperhomocysteinemia and vitamin B12 deficiency was also noticed in the probands. In the present study additional genetic variants, folate and vitamin B6, which may affect folate-homocysteine metabolic pathway, were investigated in 866 individuals including nuclear families with ADHD probands (N=221) and ethnically matched controls (N=286) to find out whether ADHD associated traits are affected by these factors. Population based analysis revealed significant over representation of MTRR rs1801394 "G" allele and "GG" genotype in all as well as male probands. Stratified analysis showed significantly higher frequency of RFC1 rs1051266 and BHMT rs3733890 "AG" genotypes in full term and prematurely delivered ADHD probands respectively. Probands with rs1801394 "GG" genotype and BHMT rs3733890 "G" allele showed association with hyperhomocysteinemia. MTHFR rs1801131, MTR rs1805087 and BHMT rs3733890 also showed association with ADHD index. While rs1051266, rs1801131, and rs1805087 showed association with behavioral problems, rs3733890 was associated with ODD score. Conduct problem exhibited association with RFC1 rs1051266, MTHFR rs1801133 and MTRR rs1801394. Gene-gene interaction analysis revealed positive synergistic interactions between rs1051266, rs1801131 and rs1801394 in the probands as compared to the controls. It can be inferred from the data obtained that folate system genetic variants and mild hyperhomocysteinemia may affect ADHD associated traits by attenuating folate metabolism.