Acetylcholine-metabolizing butyrylcholinesterase (BCHE) copy number and single nucleotide polymorphisms and their role in attention-deficit / hyperactivity syndrome

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Abstract

A previous genome-wide screen for copy number variations (CNVs) in attention deficit /hyperactivity disorder (ADHD) revealed a de novo chromosome 3q26.1 deletion in one of the patients.Candidate genes at this locus include the acetylcholine-metabolizing butyrylcholinesterase (BCHE)expressing gene (OMIM #177400), which is of particular interest. The present study investigates thehypothesis that the heterozygous deletion of the BCHE gene is associated with adult ADHD (aADHD). Ina first step, we screened 348 aADHD patients and 352 controls for stretches of loss of heterozygosity(LOH) across the entire BCHE gene to screen for the deletion. Our second aim was to clarify whetherBCHE single nucleotide polymorphisms (SNPs) themselves influence the risk towards ADHD. Putativefunctional consequences of associated SNPs as well as their un-typed proxies were predicted byseveral bioinformatic tools. 96 individuals displayed entirely homozygous genotype reads in all 12examined SNPs, making them possible candidates to harbour a heterozygous BCHE deletion. DNA fromthese 96 probands was further analyzed by real-time PCR using a BCHE-specific CNV assay. However,no deletion was found. Of the 12 tag SNPs that passed inclusion criteria, rs4680612 and rs829508were significantly associated with aADHD, as their minor alleles occurred more often in cases than incontrols (p=0.018 and p=0.039, respectively). The risk variant rs4680612 is located in thetranscriptional control region of the gene and predicted to disrupt a binding site for MYT-1, which haspreviously been associated with mental disorders. However, when examining a second independentadult ADHD sample of 353 cases, the association did not replicate. When looking up the deletion inthree genome-wide screens for CNV in ADHD and combining it with the present study, it becameapparent that 3 from a total of 1,030 ADHD patients, but none of 5,787 controls, featured a deletion ofthe BCHE promoter region including rs4680612 (p= 0.00004). Taken together, there are several linesof evidence suggesting a potential involvement of BCHE in the etiopathology of ADHD, as a rarehemizygous deletion as well as a common SNP in the same region are associated with

disease, althoughwith different penetrance. Both variations result in the disruption of the binding site of thetranscription factor MYT-1 suggesting epistatic effects of BCHE and MYT-1 in the pathogenesis ofADHD. As we were not able to replicate the SNP association, our findings should be consideredpreliminary and call for larger studies in extended phenotypes.