Association analysis of norepinephrine transporter polymorphisms and methylphenidate response in ADHD patients.

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Abstract

AIMS:
Methylphenidate (MPH) is the most frequently prescribed drug in Attention Deficit Hyperactivity Disorder (ADHD). Hitherto mostly the dopamine transporter gene has been studied in MPH-response and only a few studies analyzed the norepinephrine transporter (NET, SLC6A2) gene, although MPH is a potent inhibitor of both dopamine and norepinephrine transporters. We aimed to analyze this monoamine transporter gene in relation to ADHD per se and MPH-response in particular to gain further knowledge in ADHD pharmacogenetics using a Caucasian sample.

METHODS:
Six single nucleotide polymorphisms (rs28386840, rs2242446, rs3785143, rs3785157, rs5569, rs7194256 SNP) were studied across the NET gene in 163 ADHD children (age: 9.3±2.6; 86.5% male) using ADHD-RS hyperactivity-impulsivity and inattention scales. For case-control analysis 486 control subjects were also genotyped. At the MPH-response analysis responders had minimum 25% decrease of ADHD-RS total score after 2months of treatment, and chi-square test compared 90 responders and 32 non-responders, whereas ANOVA was used to assess symptom improvement after the first month among the 122 ADHD patients.

RESULTS:
The classical case-control analysis did not yield any association with ADHD diagnosis, which was supported by meta-analysis conducted on the available genetic data (combining previously published and the present studies). On the other hand, the intronic rs3785143 showed nominal association with inattention symptoms (p=0.01). The haplotype analysis supported this association, and indicated the importance of the first haploblock encompassing the intronic and 2 promoter SNPs. With MPH-response only the promoter rs28386840 showed nominal association: Those with at least one T-allele were overrepresented in the responder group (42% vs 19%, p=0.08), and they had better improvement on the hyperactivity-impulsivity scale compared to the AA genotype (p=0.04).

CONCLUSION:
Although none of our single SNP findings remained significant after correcting for multiple testing, our results from the MPH-response analysis indicate the potential importance of promoter variants in the NET gene.