Potential for diagnosis versus therapy monitoring of attention deficit hyperactivity disorder: a new epigenetic biomarker interacting with both genotype and autoimmunity

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Abstract

In view of the need for easily accessible biomarkers, we evaluated in ADHD children the epigenetic status of the 5′-untranslated region (UTR) in the SLC6A3 gene, coding for human dopamine transporter (DAT). We analysed buccal swabs and sera from 30 children who met DSM-IV-TR criteria for ADHD, assigned to treatment according to severity. Methylation levels at six-selected CpG sites (among which, a CGCGCGCGGG and a CGCG motif), alone or in combination with serum titers in auto-antibodies against dopamine transporter (DAT aAbs), were analysed for correlation with CGAS scores (by clinicians) and Conners’ scales (by parents), collected at recruitment and after 6 weeks. In addition, we characterized the DAT genotype, i.e., the variable number tandem repeat (VNTR) polymorphisms at the 3′-UTR of the gene. DAT methylation levels were greatly reduced in ADHD patients compared to control, healthy children. Within patients carrying at least one DAT 9 allele (DAT 9/x), methylation at positions CpG2 and/or CpG6 correlated with recovery, as evident from delta-CGAS scores as well as delta Conners’ scales (‘inattentive’ and ‘hyperactive’ subscales). Moreover, hypermethylation at CpG1 position denoted severity, specifically for those patients carrying a DAT 10/10 genotype. Intriguingly, high serum DAT-aAbs titers appeared to corroborate indications from high CpG1 versus high CpG2/CpG6 levels, likewise denoting severity versus recovery in DAT 10/10 versus 9/x patients, respectively. These profiles suggest that DAT 5′UTR epigenetics plus serum aAbs can serve as suitable biomarkers, to confirm ADHD diagnosis and/or to predict the efficacy of treatment.