SLC2A3 single-nucleotide polymorphism and duplication influence cognitive processing and population-specific risk for attention-deficit/hyperactivity disorder

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Abstract

Background
Attention-deficit/hyperactivity disorder (ADHD) is a common, highly heritable neurodevelopmental disorder with profound cognitive, behavioural, and psychosocial impairments with persistence across the life cycle. Our initial genome-wide screening approach for copy number variants (CNVs) in ADHD implicated a duplication of SLC2A3, encoding glucose transporter-3 (GLUT3). GLUT3 plays a critical role in cerebral glucose metabolism, providing energy for the activity of neurons, which, in turn, moderates the excitatory–inhibitory balance impacting both brain development and activity-dependent neural plasticity. We, therefore, aimed to provide additional genetic and functional evidence for GLUT3 dysfunction in ADHD.

Methods
Case–control association analyses of SLC2A3 single-nucleotide polymorphisms (SNPs) and CNVs were conducted in several European cohorts of patients with childhood and adult ADHD (SNP, n = 1,886 vs. 1,988; CNV, n = 1,692 vs. 1,721). These studies were complemented by SLC2A3 expression analyses in peripheral cells, functional EEG recordings during neurocognitive tasks, and ratings of food energy content.

Results
Meta-analysis of all cohorts detected an association of SNP rs12842 with ADHD. While CNV analysis detected a population-specific enrichment of SLC2A3 duplications only in German ADHD patients, the CNV + rs12842 haplotype influenced ADHD risk in both the German and Spanish cohorts. Duplication carriers displayed elevated SLC2A3 mRNA expression in peripheral blood cells and altered event-related potentials reflecting deficits in working memory and cognitive response control, both endophenotypic traits of ADHD, and an underestimation of energy units of high-caloric food.

Conclusions
Taken together, our results indicate that both common and rare SLC2A3 variation impacting regulation of neuronal glucose utilisation and energy homeostasis may result in neurocognitive deficits known to contribute to ADHD risk.