DRD3 Gene and ADHD: A Pharmaco-Behavioural Genetic Study

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Abstract

Results of candidate gene investigations in ADHD have been difficult to replicate. The complexity of the phenotypes and their underlying determinants, and the relatively small effect sizes of genetic variants may, in part, be contributing to these inconsistencies. The objective of this study is to conduct an exploratory analysis using a comprehensive approach to investigate the role of candidate genes. This approach combines a dimensional behavioural approach akin to Research Domain Criteria (RDoC), a pharmaco-dynamic evaluation of behaviours relevant to ADHD, together with association and linkage testing in a large sample of children with ADHD. Parents, teachers, and research staff evaluated children with ADHD under three experimental conditions (EC): 1 week of baseline observation, followed by 1 week of methylphenidate (MPH) and 1 week of placebo, administered in a double-blind crossover order. Several quantitative behavioural and cognitive dimensions relevant for ADHD were also assessed. We combined family-based (FBAT) and quantitative trait genetic analyses (n = 575 probands with members of their nuclear families) to investigate the role of DRD3 (Ser-9-Gly) in ADHD and its relevant behavioural dimensions. Comparing the behaviours of children with different genotypes under the three EC showed a nominal association between the T allele and poorer behavioural scores during the MPH week (as assessed by teachers), particularly in boys. With the family-based analysis, the T allele showed a nominal association with increased risk for ADHD, response to placebo and MPH as assessed by research staff, and the modulation of other behavioural and cognitive dimensions. These results provide convergent, albeit preliminary evidence for the implication of the DRD3 (Ser-9-Gly) polymorphism in the aetiology of ADHD and the modulation of its various behavioural dimensions, including RDoC cognitive constructs and response to pharmacological probes. This illustrative example suggests that this research paradigm might help to reliably uncover the role of other candidate genes in ADHD.