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Shared and unique genetic contributions to attention deficit/hyperactivity disorder and substance use disorders: A pilot study of six candidate genes

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Abstract
The shared genetic basis of attention deficit/hyperactivity disorder (ADHD) and substance use disorders (SUDs) was explored by investigating the association of candidate risk factors in neurotransmitter genes with both disorders. One hundred seven methadone maintenance treatment patients, 36 having an ADHD diagnosis, 176 adult patients with ADHD without SUDs, and 500 healthy controls were genotyped for variants in the *DRD4* (exon 3 VNTR), *DRD5* (upstream VNTR), *HTR1B* (rs6296), *DBH* (rs2519152), *COMT* (rs4680; Val158Met), and *OPRM1* (rs1799971; 118A>G) genes. Association with disease was tested using logistic regression models. This pilot study was adequately powered to detect larger genetic effects (OR≥2) of risk alleles with a low frequency. Compared to controls, ADHD patients (with and without SUDs) showed significantly increased frequency of the *DBH* (rs2519152: OR 1.73; CI 1.15–2.59; *P*=0.008) and the *OPRM1* risk genotypes (rs1799971: OR 1.71; CI 1.17–2.50; *P*=0.006).

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The *DBH* risk genotype was associated with ADHD diagnosis, with the association strongest in the pure ADHD group. The *OPRM1* risk genotype increased the risk for the combined ADHD and SUD phenotype. The present study strengthens the evidence for a shared genetic basis for ADHD and addiction. The association of *OPRM1* with the ADHD and SUD combination could help to explain the contradictory results of previous studies. The power limitations of the study restrict the significance of these findings: replication in larger samples is warranted.

1. Introduction

Both attention deficit/hyperactivity disorder (ADHD) and substance use disorders (SUDs) are quite prevalent, with estimated prevalences in the adult population of 3.4% and 9.2% respectively (Fayyad et al., 2007; Substance Abuse and Mental Health Services Administration, 2007). These disorders are highly heritable and are accompanied by substantial rates of psychiatric comorbidity. Moreover, they frequently coexist (Wilens, 2007). Although there are clear indications that the psychiatric symptoms and conduct disturbances associated with ADHD have a causative role in the development of problematic drug use and addiction (Elkins et al., 2007; Roy, 2008), there are also indications of a genetic basis for the overlap (Groman et al., 2009; Wilens, 2004). ADHD is more prevalent in families of probands with SUDs (Clark et al., 2004; Knopik et al., 2009; Marmorstein et al., 2009; Wilens et al., 2005), and SUDs are more frequent among family members of ADHD patients (Biederman et al., 1992; Faraone et al., 2000; Milberger et al., 1998). Indeed, a study assessing both ADHD and SUDs in families of ADHD probands revealed evidence for a shared familiality of ADHD and drug use disorders with variable expression (Biederman et al., 2008).

The genetic risk factors common to ADHD and SUDs have not yet been identified, mostly because the etiologies of the two disorders are still largely unknown. The most attention has been focused on neurotransmitter systems involved in the pathophysiology of the two disorders, especially the dopaminergic system; dopamine is the primary neurotransmitter of the central motivation system, which plays a crucial role in addiction (Koob and Volkow, 2010; Volkow et al., 2009). Dopamine is also implicated in ADHD, mainly due to the therapeutic effects of stimulant medication, which inhibits the reuptake of dopamine (Biederman and Faraone, 2005; Tripp and Wickens, 2009). Serotonin dysregulation is also hypothesised to play a causal role in ADHD and addiction (Oades, 2008; Ribases et al., 2009; Ross and Peselow, 2009). Genetic determinants of variability in these neurotransmitter systems have been studied in both disorders, with controversial results (Faraone et al., 2005; Kreek et al., 2005; Yuferov et al., 2010). In cases where particular variants conveying an increased risk were described, the results have proven difficult to reproduce. This is because the impact of each variant is quite small, attesting to the polygenic nature of the two disorders (Faraone and Mick, 2010; Wong and Schumann, 2008).

Direct comparison studies of risk genotypes in different patient populations are rather scarce. A recent assembly of both clinical and genetic data from different populations allowed us to explore the role of a limited number of genetic polymorphisms in the proposed shared predisposition to ADHD and SUDs. Due to the limited size of the project, a pragmatic choice was made to study six well-documented polymorphisms of the genes *DRD4*, *DRD5*, *HTR1B*, *DBH*, *COMT*, and *OPRM1*, previously used in association studies of ADHD and/or SUDs. It is important to point out that most family studies on the genetics of ADHD (indeed, most of the studies mentioned below) were carried out in child and adolescent populations. However the available scientific information indicates that the heritability of clinically diagnosed childhood and adult ADHD is quite similar. Moreover results of candidate gene as well as genome-wide molecular genetic studies in adult ADHD samples implicate some of the same genes involved in ADHD in children, although in some cases different alleles and different genes may be responsible for adult versus childhood ADHD (Franke et al., 2011).

The dopamine D4 and D5 receptors are well represented in the frontal–subcortical networks implicated in the pathophysiology of ADHD, as shown by neuroimaging and neuropsychological studies (Brennan and Arnsten, 2008; Curatolo et al., 2009). Most molecular genetic studies of *DRD4* in ADHD have focused on a variable number of tandem repeat polymorphisms (VNTRs), which consist of a 48 base-pair (bp) repeat unit that codes an amino-acid sequence located in the third cytoplasmic loop of the receptor. This sequence is thought to be involved in G-protein coupling (DiMaio et al., 2003). The association of the 7-repeat allele with ADHD has been confirmed in three meta-analyses (Faraone et al., 2005; Gizer et al., 2009; Li et al., 2006), and was used as the risk allele in this study. The *DRD4* polymorphism has not been studied extensively in substance use disorders, except for a Hungarian study of addicted patients which failed to reveal a significant association with addiction (Szilagyi et al., 2005). The most widely studied polymorphism, our choice for this study, of the dopamine D5 receptor (*DRD5*) is a dinucleotide repeat that maps approximately 18.5 kb upstream of the transcription start site (Hawi et al., 2003). The common 148-bp repeat allele is clearly associated with ADHD (Gizer et al., 2009; Li et al., 2006; Lowe et al., 2004; Maher et al., 2002). No significant association of this allele with SUDs has yet been identified (Le Foll et al., 2009).

Serotonin dysregulation has been related to impulsive behaviour (Dalley et al., 2008) and thus hypothesised to play a causal role in ADHD. A modest but significant association between ADHD and a G>C transition at nucleotide position 861 (861G>C; rs6296) of the serotonin 1b receptor (*HTR1B*; 5-HT1B) gene has been confirmed in a recent meta-analysis (Gizer et al., 2009; Hawi et al., 2002)