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Review

Psychopathological aspects of dopaminergic gene polymorphisms in adolescence and young adulthood

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ABSTRACT

Dopamine hypotheses of several psychiatric disorders are based upon the clinical benefits of drugs affecting dopamine transporter or receptors, and have prompted intensive candidate gene research within the dopaminergic system during the last two decades. The aim of this review is to survey the most important findings concerning dopaminergic gene polymorphisms in attention deficit hyperactivity disorder (ADHD), Tourette syndrome (TS), obsessive compulsive disorder, and substance abuse. Also, genetic findings of related phenotypes, such as inattention, impulsivity, aggressive behavior, and novelty seeking personality trait are presented, because recent studies have applied quantitative trait measures using questionnaires, symptom scales, or other objective endophenotypes. Unfortunately, genetic variants with minor effects are problematic to detect in these complex inheritance disorders, often leading to contradictory results. The most consistent association findings relate to ADHD and the dopamine transporter and the dopamine D4 receptor genes. Meta-analyses also support the association between substance abuse and the D2 receptor gene. The dopamine catabolizing enzyme genes, such as monoamine oxidase (MAO) A and catechol-*O*-methyltransferase (COMT) genes, have been linked to aggressive behaviors.

Contents

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1. Introduction

Family, twin, and adoption studies indicate that a substantial inherited component exists in the background of many psychiatric disorders. Deciphering the specific genetic risk factors of a certain psychiatric disorder is expected to reveal the neurobiology of the disorder and the related atypical behaviors. Analyzing genetic and environmental risk factors and their interactions, which may lead to these complex inheritance disorders, is the aim of many psychiatric genetics studies. Despite intense research efforts during the last two decades, understanding the fundamental changes that result in psychopathologies is still a challenge for researchers (Burmeister et al., 2008). Using the dimensional approach seems to be more powerful than using disease categories, and this trend is apparent in the new diagnostic manuals, i.e., in the DSM-V (Diagnostic and Statistical Manual of Mental Disorders 5th edition) and in the ICD-11 (International Classification of Disease 11th edition), that are currently under preparation (Andrews et al., 2009). Disorders can be regarded as extremes of a spectrum, and this view supports the growing importance of using quantitative trait analyses in clinical areas (Plomin et al., 2009). Identifying intermediate phenotypes, termed endophenotypes, is also helpful in the assessment of specific genetic factors in heterogeneous disorders (Almasy and Blangero, 2001).

Epidemiological studies have shown large genetic part in the pathogenesis of many childhood-onset psychiatric disorders. For example, in attention deficit hyperactivity disorder (ADHD), which is one of the most common childhood psychiatric disorders and can persist through adolescence and adulthood, the heritability estimates range from 60% to 90% (Faraone et al., 2005). The picture is complex, however, as the genetic background is polygenic, and genetic factors may interact with each other and with environmental factors. Multifactorial, polygenic inheritance has been proposed for most neuropsychiatric disorders, even for those that have a 90% or higher heritability estimate, such as autism or Tourette syndrome (TS), since no single gene with a major effect has been convincingly identified to date in these disorders (Pauls, 2001; Happe et al., 2006). Until now, dopamine and serotonin neurotransmitter systems have been studied mainly in child and adolescent psychopathologies; however, novel theories point to the importance of neuroprotective factors, cell adhesion molecules, and components involved in synapse formation (Cichon et al., 2009). To focus our review, only the dopamine system findings will be discussed in detail, because the developmental changes of this neurotransmitter system seem to correspond to the onset of the presented psychiatric disorders. In the primate cortex, dopamine receptor densities peak in childhood and elevated dopaminergic activity is observed during adolescence (Wahlstrom et al., 2010). Dopaminergic pathways affect a range of cognitive and executive functions, such as working memory or behavioral flexibility linked to prefrontal cortex (PFC) activity (Floresco and Magyar, 2006), as well as positive reinforcement and reward mechanism related to the limbic system (Sesack and Grace, 2010). Among other monoamine neurotransmitters, dopamine also has an important role in impulsive behaviors (Pattij and Vanderschuren, 2008). In this review, we present dopaminergic genetic findings of childhood-onset psychiatric disorders that persist during adolescence (e.g., ADHD, TS) and of psychiatric disorders which are diagnosed later in adolescence (e.g., obsessive compulsive disorder, substance abuse). Quantitative traits, like impulsivity, and objective endophenotypes, like sustained attention performance are also discussed.

2. Dopaminergic candidate genes

2.1. Candidate genes vs. whole genome search

Heritability, defining the proportion of the variance explained by genetic factors in certain phenotypes (traits or symptoms), is estimated by comparing the concordance rates of monozygotic and dizygotic twin pairs (Glatt et al., 2008). To identify the specific genes accounting for the heritability, two major methods are currently applied that supplement each other. Candidate gene analyses can reveal the actual genetic variants of the protein-coding genes that are implicated in the pathophysiology of the disorder (Glatt et al., 2008). Based on neurobiological theories, polymorphisms in the monoamine (dopamine, norepinephrine, and serotonin) receptor and transporter genes are the most widely studied candidate genes in psychiatric genetics. The alternative strategy aims to identify specific chromosomal regions that are related to the disorder by analyzing the whole genome without an *a priori* hypothesis. Linkage studies analyze marker polymorphisms throughout the genome in extended pedigrees of patients to find chromosomal region(s) linked to the disorder. A major genetic effect is identified as a cosegregation of a marker variant (allele) and the disorder with a logarithm of odds (LOD) score of higher than 3 (Lander and Kruglyak, 1995). Whereas this strategy is highly powerful for monogenic diseases, it has proven less effective for complex inheritance disorders in which the individual genetic factors have small effects. Genome-wide association studies (GWAS) are a recent approach of whole genome searches. These studies aim to identify common genetic variants with a relative risk of 1.1–1.4 by studying thousands of patients and control subjects (Cichon et al., 2009). Because single studies using either approach cannot identify definite genetic risk alleles unambiguously, meta-analyses combine the samples to gain a higher power of analysis. Among childhood-onset disorders, ADHD and autism have been assessed by GWAS, resulting in numerous novel putative candidate genes (Franke et al., 2009; Weiss, 2009), and the first GWAS in obsessive compulsive disorder (OCD) and TS are presently underway (Grados, 2010). Although the first meta-analysis of ADHD GWAS has not been able to identify any significant genome-wide association (Neale et al., 2010), the conclusion is probably just as important: If common genetic variants account for the majority of the genetic component in the pathogenesis of a disorder, then their effect sizes must be very small. The alternative explanation would be that mostly rare genetic variants (different in every patient but might effect the same neurobiological pathway) account for the heritable component. A new concept for future genetic studies emphasizes the underlying traits in psychiatric disorders which can be expressed as variations in brain functioning. Certain gene variants influence the traits and not the disorder. The risk to develop a disorder comes from the combination of these traits (Hudziak and Faraone, 2010). Therefore, in this review, we mention not only the categorical, psychiatric disorder based association studies (third section), but also those genetic association studies which used quantitative traits (fourth section). Wherever possible, gene × gene interaction findings are indicated,