

# Molecular genetic aspects of attention-deficit/hyperactivity disorder

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Received 16 May 2004; revised 7 September 2004; accepted 8 September 2004

## Abstract

Two genome wide scans, one of which was subsequently extended, have led to the identification of different chromosomal regions assumed to harbour genes underlying attention-deficit/hyperactivity disorder (ADHD). Some of these regions were also identified in patients with autism and/or dyslexia. The only region for which both studies detected a LOD score  $> 1$  was on chr 5p13 which is in the vicinity of the location of the candidate gene DAT1. The candidate gene approach has revealed the most robust and replicated findings for DRD4, DRD5, and DAT1 polymorphisms. Meanwhile interesting endophenotype studies have also been conducted suggesting a genetic basis for different diagnostic and therapeutic criteria. Animal studies for ADHD have investigated especially hyperactivity and have focused mainly on knockout and QTL designs. In knockout mice models the most promising results were obtained for genes of the dopaminergic pathway. QTL results in rodents suggest multiple loci underlying different forms of natural and induced hyperactivity. The molecular results mentioned above are presented and discussed in detail, thus providing both clinicians and geneticists with an overview of the current research status of this important child and adolescent psychiatric disorder.

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**Keywords:** Attention-deficit/hyperactivity disorder (ADHD); Hyperkinetic syndrome; Hyperactivity; Attention deficit; Impulsivity; Genome scan; Candidate gene; Polymorphism; Endophenotype; Knockout; Quantitative trait loci (QTL); Dopamine

## 1. Introduction

### 1.1. Definition of the syndrome and diagnostic criteria

Attention-deficit/hyperactivity disorder (ADHD) is currently diagnosed according to the DSM-IV-TR criteria [1]. The predominantly inattentive, predominantly hyperactive/impulsive or combined type is diagnosed if a threshold number of symptoms of inattention and/or hyperactivity/impulsivity apply. As for any other psychiatric disorder, we need to consider the possibility that the diagnostic criteria including the delineation of these three different types might be suboptimal with respect to the elucidation of the molecular genetic basis of the underlying biologically relevant traits. This concern applies particularly to ADHD, because the most frequent combined type is based on symptoms, which represent the upper and lower ends of

**Abbreviations:** 5-HTR1B, 5-hydroxytryptamine receptor 1B; 5-HTT, 5-hydroxytryptamine (=serotonin) transporter; 5-HTTLPR, 44-bp deletion in the promoter region of the serotonin transporter; ADHD, attention-deficit/hyperactivity disorder; bp, base pair; c-c, case-control; chr, chromosome; cM, centi Morgan; COMT, catechol-0-methyltransferase; DAT1, dopamine transporter 1 (solute carrier family 6, member 3 (SLC6A3)); DBH, dopamine  $\beta$ -hydroxylase; DRD, dopamine receptor; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; EDTD, extended transmission/disequilibrium test; F2, generation 2; HHRR, haplotype-based haplotype relative risk; HRR, haplotype relative risk; LD, linkage disequilibrium; LOD, logarithm of the odds; MAOA, monoamine oxidase A; MPH, methylphenidate; QTL, quantitative trait loci; R, repeat; RI, recombinant inbred; SNPs, single nucleotide polymorphisms; TDT, transmission disequilibrium test; VNTR, variable number tandem repeat.

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the seemingly unrelated quantitative distributions for activity and attention, respectively. Thus, from a genetic viewpoint, it might be argued that a separate analysis of these two quantitative traits might be more straightforward.

Their joint analysis and hence of the disorder as such is, however, warranted because inattention and hyperactivity co-occur considerably more frequently than can be expected by chance. Thus, in unselected twins correlations of 0.6–0.9 have been reported for symptoms of inattention and hyperactivity [2]. Furthermore, both twin and family studies indicate that the type does not breed true. Thus, a specific type in one twin of a monozygotic twin pair (MZ) does not predict the type in the second twin [3,4]. Within pedigrees, affecteds can have any one of the types [5,6]; no familial clustering of a particular type occurs.

As with any other psychiatric disorder, the reliability and validity of the diagnostic criteria are of crucial importance for studies attempting to identify the molecular basis of ADHD. The rater-effect, which has repeatedly been observed for ADHD [3,7,8], could lead to different heritability estimates depending on the respective informant. Whereas the estimates based on different informants are largely within the same range [7,8], the fact that the same child can be rated very differently with respect to the core symptoms of ADHD by mothers, fathers, teachers and clinicians, underscores the need to use an as uniform as possible phenotypical assessment procedure.

ADHD according to DSM-IV-TR is a categorical diagnosis. At the same time the use of a threshold number of symptoms to define hyperactivity, impulsivity and inattention clearly indicates that these core phenotypes are viewed dimensionally. For the initiation and interpretation of both formal and molecular genetic studies it is important to distinguish a categorical vs. a dimensional conceptualisation of ADHD and to realize the potential advantages and disadvantages of both approaches.

Findings indicative of cross-cultural differences in prevalence rates of ADHD [9] potentially suggest that the frequency of predisposing (and/or protective) genotypes differs across the world. However, caution is warranted because such differences in prevalence rates might at least partially be due to culturally divergent ratings of ADHD symptoms [10] and/or to socio-cultural influences on relevant clinical symptoms.

### 1.2. Formal genetic studies and heritability estimates

Several formal genetic studies have addressed the contribution of both genetic and environmental factors to the development of ADHD using both categorical and dimensional definitions. Twin studies, for example, have come up with concordance rates between about 50 and 80% for MZ twins vs. 30–40% for DZ twins [11]. MZ and DZ correlations for quantitative traits of ADHD of between 0.48 and 0.92 and  $-0.16$  and  $0.57$ , respectively, also indicate substantial heritability (for review see Ref. [11]).

Based on these results, heritability of ADHD is estimated at approximately 0.8 [12].

The importance of genetic factors in the etiology of ADHD is also supported by the results of adoption studies: biological parents and sibs of an ADHD-child are significantly more often affected by ADHD (and comorbid disorders) than the adoptive parents and sibs [11,13–15].

According to DSM-IV, comorbid disorders are diagnosed separately. However, it is conceivable that the genetic factors underlying inattention and/or hyperactivity/impulsivity at the same time predispose to other psychopathological or cognitive symptoms in subgroups of ADHD patients. Hence the comorbidity might be useful for defining these genetically potentially more homogeneous subgroups. Indeed, formal genetic evidence suggests that in genetic terms ADHD with and without comorbid conduct disorder differ [16–18]; conduct disorders, but not affective and anxiety disorders, cosegregate within families [18].

### 1.3. Heterogeneity in ADHD

The recent results of genome wide linkage analyses have detected single chromosomal peak regions which overlap with those identified previously for autism and/or reading disorders [19–28]. Whereas it is currently unknown if these overlapping regions indeed indicate a gene(s) predisposing to more than one disorder, we need to keep this possibility in mind. Optimally, phenotyping should include careful assessment of comorbid disorders. Such extensive evaluations are however costly and thus have a negative impact on case numbers given a specified amount of research funds. Furthermore, future research might point to endophenotypes that from a current viewpoint do not seem a top priority.

In this context the high ADHD prevalence rate of approximately 3–10% [29–31] in itself suggests that the disorder is not homogeneous. As in other complex disorders, it is likely that in etiological and in particular in genetic terms distinct types of ADHD exist; this is particularly the case if infrequent monogenic forms of ADHD exist. The more polygenic the disorder is, the more alleles will not only overlap between affecteds; they will also occur with albeit lower frequency in unaffecteds. If and to what extent all these different (overlapping) types can be differentiated at the phenomenological level is a matter of debate. The recent elucidation of mutations in the melanocortin-4 receptor gene as a cause of obesity in 2–4% of obese children shows that such a delineation is not necessarily always possible [32].

Molecular analyses of quantitative traits can benefit substantially from ascertainment schemes which concentrate on those individuals with the most extreme concordant and/or discordant phenotypes [33]. Indeed, ADHD symptoms have been assessed dimensionally both in studies of heritability (e.g. [2]) and in gene localization studies [34]. In this context, it would seem helpful to know more about the quantitative distribution of the relevant traits in the general

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