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REVIEW

Molecular genetics of attention-deficit/hyperactivity disorder: an overview

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Abstract As heritability is high in attention-deficit/hyperactivity disorder (ADHD), genetic factors must play a significant role in the development and course of this disorder. In recent years a large number of studies on different candidate genes for ADHD have been published, most have focused on genes involved in the dopaminergic neurotransmission system, such as DRD4, DRD5, DAT1/SLC6A3, DBH, DDC. Genes associated with the noradrenergic (such as NET1/SLC6A2, ADRA2A, ADRA2C) and serotonergic systems (such as 5-HTT/SLC6A4, HTR1B, HTR2A, TPH2) have also received considerable interest. Additional candidate genes related to neurotransmission and neuronal plasticity that have been studied less intensively include SNAP25, CHRNA4, NMDA, BDNF, NGF, NTF3, NTF4/5, GDNF. This review article provides an overview of these candidate gene studies, and summarizes findings from recently published genome-wide association studies (GWAS). GWAS is a relatively new tool that enables the identification of new ADHD genes in a hypothesis-free manner. Although these latter studies could be improved and need to be replicated they are starting to implicate processes like neuronal migration and cell adhesion and cell division as potentially important in the aetiology of ADHD and have suggested several new directions for future ADHD genetics studies.

Keywords Genetics · ADHD · Candidate gene studies · GWAS · Aetiology

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common, clinically heterogeneous (in terms of co-morbidities, gender effects, courses and outcomes), etiologically complex disorder characterized by early onset of age-inappropriate persistent and pervasive symptoms of inattention, hyperactivity, and impulsivity; twin and adoption studies show ADHD to be highly heritable, i.e., a heritability of around 0.76 [53]. Converging evidence from animal and human studies

implicates the dysregulation of frontostriatal and frontocerebellar catecholaminergic circuits in the pathophysiology of ADHD [18]. In addition to prefrontal cortical areas, the basal ganglia, cerebellum, temporal and parietal cortex have been implicated in this condition [27, 141]. ADHD is associated with various neuropsychological alterations, such as deficits in vigilance-attention, cognitive control, namely executive function deficits, non-executive memory deficits, and motivation, namely delay aversion, as well as millisecond timing deficits, state regulation failures, intra-individual fluctuations in performance over time, and an altered sensitivity to stimulation [142, 163].

Up to now more than 1,800 publications, dealing with the genetics of ADHD, have been published and the following review will be representative and comprehensive, but not exhaustive, and is meant to give the reader an overview of current findings from genetic association studies of this disorder including both candidate gene studies and genome-wide association studies (GWAS). Studies on gene-environment interaction in ADHD are not included in this overview, but are reviewed in another article in this edition [186]. For the detection of small effects of individual genes, such as those likely to occur in ADHD, genetic association studies [144] are generally more suitable than genetic linkage analyses. However, population stratification differences between case and control samples can give rise to both type I and II errors if case and control samples are not well matched for ethnic background. Linkage studies have been extremely successful in elucidating the causes of monogenic disorders, but much less so in multifactorial disorders. ADHD linkage studies have identified a number of genetic loci (potentially) harbouring genes for ADHD and some chromosome regions such as 5p13, 14q12, and 17p11 have been indicated in multiple studies [3, 7, 9, 50, 54, 73, 96, 131, 146]. In the most recent meta-analysis of seven ADHD linkage studies, genome-wide significant linkage was only confirmed for one locus on chromosome 16 [196].

Until recently, association approaches were restricted to hypothesis-driven studies on candidate genes, as described in the following paragraphs. Such approaches are substantially influenced by the amount of existing knowledge regarding disease aetiology. Since this knowledge is still limited for ADHD, candidate gene based studies are likely to miss at least part of the genetic variance. Up to now, such studies can explain no more than 3–5% of the total genetic components of ADHD [98]. At the end of 2008, the first unbiased, hypothesis-free GWAS were published for ADHD, these will be reviewed below, after the candidate gene studies.

Candidate gene approaches

Genes belonging to the dopaminergic neurotransmission system—in particular the D4 dopamine receptor gene (*DRD4*) and the human dopamine transporter gene (*DAT1/SLC6A3*)—have been the most frequently investigated genes. In addition, genes of the noradrenergic and the serotonergic system have also been frequently studied. To date, individual gene variants have only shown small effects, rarely reaching an odds ratio of 1.3 (e.g. [53], a figure consistent with that obtained from meta-analyses of other complex traits [78].

Dopaminergic system

The effectiveness of methylphenidate, which acts by blocking the dopamine transporter, in ADHD treatment as well as the association of ADHD with those executive neuropsychological functions and frontostriatal pathways, that are dependent on an intact dopaminergic neurotransmission make the dopaminergic system the most intensively analyzed neurotransmitter system in ADHD [166].

D4 dopamine receptor gene (DRD4)

The association between ADHD and a 48 base-pair (48 bp) repeat polymorphism of exon III of the *DRD4* gene—encoding a receptor expressed primarily in the prefrontal cortex—is the strongest and most consistently replicated molecular genetic finding in ADHD. A meta-analysis of more than 30 studies found that the *DRD4* 7-repeat (DRD4-7r) allele increases the risk for ADHD, although this increase is only moderate with a pooled odds ratio of 1.34 [51, 98]. Importantly this finding was supported in Caucasian as well as several non-Caucasian populations [10, 17, 29, 66, 194]. In functional terms the *DRD4* 7-repeat allele seems to alter the function of the encoded receptor by making it less sensitive to dopamine than the alternative alleles [5].

Studies of the cognitive correlates of the DRD4 7-repeat allele in ADHD have found mixed results. A hypothesis that the *DRD4* 7-repeat allele is particularly associated with inattentiveness rather than hyperactivity or impulsivity, has not yet been consistently confirmed [88, 120, 180]. Swanson et al. [165] were the first to report that carrier of at least one 7-repeat allele with ADHD did not display neuropsychological deficits. Moreover, the subgroup of probands with ADHD but without a 7-repeat allele (non-carriers) showed longer reaction times. Therefore, the 7-repeat allele might be associated with behavioural features rather than cognitive deficits. These findings were confirmed by the results of Manor and colleagues [117] and

Bellgrove and colleagues [16], who showed that children with ADHD with the 7-repeat allele exhibit better commission and omission scores and lower reaction time variability. Johnson et al. [79] support this hypothesis with a spectral analysis of reaction time variability revealing that absence of the 7-repeat allele is associated with drifting sustained attention resulting in inconsistent performance within a larger sample of Irish children with ADHD. Contrary to these findings, Langley and colleagues [93] report that carriers of the 7-repeat allele showed greater impulsiveness (faster reaction time) than non-carriers; Waldman et al. [179] referred to longer reaction times for homozygous carriers of the 7-repeat allele and Kieling et al. [82] described that presence of the 7-repeat allele was associated with more commission errors during a continuous performance task (CPT). Finally, Barkley and colleagues [12] reported no differences across a range of tests. However, in summary association of high reaction time variability with the 7-repeat allele absence appears to be the most consistent result and seems to be specific to ADHD [81]. The overall importance of these studies seeking to link genotype with neuropsychological functioning are limited by a range of methodological issues the most important of which are, relatively small sample sizes, a failure to account for the neuropsychological heterogeneity of ADHD, a lack of standardisation of neuropsychological tasks between studies and the use of clinically focused tasks rather than tasks that are based in neuroscience [33]. For a more detailed review of the relationship between candidate genes for ADHD and neuropsychological phenotypes see [81].

Regarding correlates between specific *DRD4* genotypes and structural anatomical findings, Durston et al. [44] suggested that variations in *DRD4* influence prefrontal grey matter volume in a sample of subjects that included individuals with ADHD as well as their unaffected siblings, and healthy controls. Monuteaux et al. [125] also reported findings in adults with ADHD showing that 7-repeat allele carriers have a significantly smaller mean volume in the superior frontal cortex and cerebellum cortex when compared to subjects without this particular allele. Whilst Shaw et al. [156] found that carrying the *DRD4* 7-repeat allele was associated with having a thinner right orbitofrontal/inferior prefrontal and posterior parietal cortex—regions overlapping those found to be thinner in ADHD—this same group were found to have better clinical outcomes. They also had a distinct trajectory of cortical development with a normalization of right parietal cortical thickening during adolescence. This has also previously been linked to having a better clinical outcome. However, two other studies reported that possession of the *DRD4* 7-repeat allele was associated with greater persistence of ADHD over time [92]. Based on the finding that 7-repeat allele carriers more likely exhibit antisocial behaviour, an alternative hypothesis has been proposed which suggests that possession of the *DRD4* 7-repeat allele influences the association between ADHD and conduct disorder [76].

The most frequently investigated gene × gene or marker × marker interaction in ADHD is the interaction of *DRD4* (7-repeat allele) and *DAT1* (10-repeat allele; see below). Based on results of two studies on Chilean families, Carrasco et al. [26] and Henriquez et al. [74] suggested that neither the *DRD4* 7-repeat nor the *DAT1* 10-repeat allele result in genotype frequency differences between affected children and their healthy siblings. However, the simultaneous presence of both, *DRD4* 7-repeat heterozygosity and *DAT1* 10-repeat allele homozygosity was more frequent in affected children as compared to their healthy siblings. Qian et al. [135] failed to replicate these initial findings. A fourth study which tried to confirm the interaction in a Mexican sample revealed no association with ADHD, neither for the individual markers nor for their combination [59]. Kebir et al. [81] analysed these markers and their relationship to IQ in a French sample. Besides their not detecting an association, they suggest that the verbal quotient as a specific domain of the IQ is correlated to the level of externalizing behaviour in boys with ADHD who carry the risk genotypes of both markers. In fact Mill et al. [122] were the first to suggest that DRD4 (and DAT1) exert their effects on ADHD by influencing IQ in a population-based sample, although it should be noted that Sonuga-Barke et al. [161] were unable to replicate these findings in the sample of the International Multi-centre ADHD Gene (IMAGE) project. In sum, the publications on gene × gene interactions are inconclusive and require further investigations in much larger samples or a meta-analysis to rule out false conclusions.

Other dopamine receptors

The 148 bp allele of a dinucleotide $(CA)_n$ repeat polymorphism located 18.5 kb 5′ of the dopamine D5 receptor gene (*DRD5*), has also received considerable attention. While two meta-analyses supported an association with ADHD (pooled odds ratio ~1.3) [98, 112], Mill et al. [123] and Loo et al. [110] found no evidence for a relationship between *DRD5* status and a range of cognitive endophenotypes of ADHD in samples of moderate size (for a more detailed discussion of the endophenotype approach see below). Recently, Langley et al. [92] reported an association of the 148 bp allele with persistence of ADHD from childhood to adolescence in a longitudinal study.

Allelic variants of the dopamine D1, D2 and D3 receptors have also been investigated with conflicting results. A first study reported evidence for an association between variants of *DRD1* and ADHD. The receptor

encoded by this gene is mainly located in the prefrontal cortex and in the striatum and it was suggested that it may modulate working memory capacity and may be associated specifically with inattention. The re-analysis of genotype data of a GWAS of the IMAGE sample revealed nominal significance of single nucleotide polymorphisms (SNPs) in *DRD1* for association to ADHD [130] as well as an association to time-to-onset of ADHD [94]. Two polymorphisms in the non-translated 5′ region and one marker in the non-translated 3′ region were associated with an increased risk for ADHD (odds ratio ~1.3, each) [124]. This particular finding, however, was not replicated in a candidate study in the IMAGE sample [21]. An association of *DRD2* SNPs with CPT phenotypes in ADHD has been brought up by Kollins et al. [87]. Moreover, there is also some evidence for an involvement of the dopamine D3 receptor gene (*DRD3*) in the aetiology of ADHD: Guan et al. [65] reported a nominally significant association in a Chinese Han population, whereas the results of Davis et al. [37] indicate a role of the *DRD3* in the manifestation of hyperactive/impulsive symptoms of ADHD. However, the findings concerning both *DRD2* [87, 120, 180] and *DRD3* [21, 37, 120, 180] are inconsistent and require further investigation in independent samples.

Dopamine transporter gene (DAT1/SLC6A3)

The dopamine transporter is expressed primarily in the striatum and the nucleus accumbens and is a site of action of methylphenidate. Consequently, the association between ADHD and variations in the *DAT1* gene has been extensively studied. The *DAT1* gene contains a 40 bp variable number tandem repeat (VNTR) polymorphism in the non-translated 3′ region. The 9-repeat allele (440 bp) (23.4%) and the 10-repeat allele (480 bp) (71.9%) are the most frequent alleles [177] in Caucasian populations. The 10-repeat allele is possibly related to an increased mesolimbic expression of the transporter [177].

Although there have been many reports supporting a positive association between *DAT1* and ADHD, there are also negative findings. A recent meta-analysis found a significant heterogeneity between family-based European association studies (stronger effects) and Asian case–control studies (weaker effects), and did not support an overall significant association between *DAT1* and ADHD [98]. Further evidence of possible ethnicity effects comes from studies that indicated associations in case–control studies in Afro-Caribbean subjects [10] which were not detected in Middle-Eastern subjects [10]. Similarly, a small Indian family study found evidence for association of ADHD and the shorter 9-repeat allele rather than the 10-repeat allele usually found to be associated with ADHD in other studies [36]. Another group has suggested that the 10-repeat allele of *DAT1* is associated with increased risk for ADHD only in the presence of another functional variant. In two studies they found increased risk only if a combination of the 10-repeat allele and a 6-repeat allele of a 30-bp VNTR in intron 8 of the *DAT1* gene were both present [6, 23]. Whereas Brüggemann and co-workers [25] did not find an association for this haplotype with the adult form of ADHD, Franke et al. [55] reported that the 9–6 haplotype rather than the 10–6 haplotype is more likely to be associated with childhood ADHD. This finding was recently replicated in a sample of 1,440 ADHD cases which persisted into adulthood and 1,769 controls from the International Multicentre persistent ADHD CollaboraTion (IMpACT) project [57]. In a Brazilian sample, Genro et al. [61, 62] found preferential transmission of a common haplotype in the 5′ region to offspring with ADHD whereas they found no association to any haplotype in the 3′ region of the gene. Recently, further evidence for the presence of at least two loci associated with ADHD within the *DAT1* was described. While Friedel et al. [58] detected a haplotype spanning the first three introns of the gene with relative risks of 1.95 and 2.43 for heterozygous and homozygous carriers, respectively, Brookes et al. [24] replicated their initial association of SNPs at the 5′ end of the gene and identified a haplotype spanning the 5′ and 3′ markers. Underlining these observations, Xu et al. [193] report an association of genetic variation in the promoter region of *DAT1* with ADHD in samples from both the UK and Taiwan. Zhou et al. [195] suggested that the presence or absence of conduct disorder might influence the association of DAT1 with ADHD. They analysed genotypes of 20 DAT1 markers in 576 trios, 141 of whom had comorbid conduct disorder and found that *DAT1* was only associated with ADHD when conduct disorder was not present; interestingly two independent association signals were present in ADHD without CD (but not ADHD + CD) at both, the 5′ and 3′ end of the DAT1 gene. In addition, three studies suggested that the genetic associations to ADHD and in particular those for *DAT1* may depend on gender: While the effect sizes for the ADHD association observed by Biederman et al. [19] were stronger when stratified by sex, e.g. for *DAT1* in males, Hawi et al. [72] reported paternal over-transmission of risk alleles for ADHD, especially for the VNTR in the 3′ non-translated region. A second study of the same group in 1,248 ADHD nuclear families also provided support for a parent of origin effect for the intron 8 and 3′ non-translated region VNTRs as well as the paternal risk haplotype of both [71]. Exploring parent of origin effects in the IMAGE sample, Anney et al. [2] found no evidence to support an overall parent of origin effect for 554 independent markers of 47 ADHD candidate genes, including markers in *DAT1*. Based on these contradictory findings further studies of the association of the

DAT1 alleles and ADHD in large datasets that allow investigating the role of age-related changes, ethnicity and gender effects, gene-environmental interactions, parent of origin effects, and the influence of comorbidity patterns are needed.

Regarding structural anatomical correlates, Durston et al. [44] reported that *DAT1* variability influences caudate, but not prefrontal cortex volume. A functional imaging study suggested that the *DAT1* genotype affects activation in the striatum and cerebellar vermis and that the familial risk of ADHD is related to the striatum but not to the vermis which requires further support [45].

There is also evidence that variations in the *DAT1* gene have a significant effect on aspects of executive neuropsychological functioning [80]. Significant genotype effects were found for performance on the "Tower of London" and on the "Wechsler Intelligence Scale for Children Freedom From Distractibility Index"; children with ADHD with the 9-repeat/10-repeat genotype exhibited poorer performance on these measures as compared to children with the 10-repeat/10-repeat genotype [80]. Contrary to these findings, Bellgrove et al. [14] found that ADHD patients with the 10-repeat/10-repeat genotype had a greater attentional bias in a CPT than those with the other allele combinations. Barkley et al. [12] again found effects of *DAT1* status on neuropsychological functioning, but only in their control group where those with the 9-repeat/10-repeat genotype performed less well on a CPT. Also, Loo et al. [110] detected no relationship between *DAT1* status and a range of cognitive performance measures in children with ADHD. A systematic review of studies investigating links between the VNTR in the 3′ untranslated region of the *DAT1* and neurophysiological and neuropsychological measures concluded that the majority of studies did not find a relation between *DAT1* and either of these measures [148]. An associated study of 350 children and adolescents with ADHD and 195 non-affected siblings using a broad set of executive/cognitive and motor tests concluded that whilst several of the *DAT1* polymorphisms were associated with ADHD and whilst ADHD was associated with impaired neuropsychological functioning, none of the *DAT1* polymorphisms was convincingly associated with neuropsychological dysfunctions [148]. As before the relevance of the studies investigating potential links between genotype and neuropsychological functioning are limited by design issues.

The DAT1 gene may also influence the response to medication. Thus, Loo et al. [111] reported that DAT1 alleles may mediate medication-related EEG changes in ADHD, with children with ADHD and two copies of the 10-repeat allele showing increased and 9-repeat carriers with ADHD showing decreased cortical activation and arousal after a single 10-mg dose of methylphenidate.

Other dopaminergic genes

No clear evidence has been reported to support an association between ADHD and variations in the tyrosine hydroxylase gene (*TH*), which catalyzes the conversion of tyrosine to dopa. Ribases et al. [143] found the dopamine decarboxylase gene (*DDC*)—whose enzyme is responsible for catalyzing the conversion of dopa to dopamine and L-5 hydroxytryptophan to serotonin—to be strongly associated with both adult and childhood ADHD. Two further studies support this finding: one analysis of the IMAGE data [95] as well as a study on a Chinese Han sample also found a nominally significant association [65]. There are, however, also negative results from an earlier analysis that included a subsample of patients from the IMAGE sample [21].

Several studies have reported an association between ADHD and a polymorphism (TaqI) of the dopamine beta hydroxylase gene (*DBH*) that encodes for the enzyme that catalyzes the conversion of dopamine to noradrenaline (pooled odds ratio $\sim$1.3). However, there were differences between studies with increased risk being associated with the A2 allele in some studies, but with the A1 allele in others [120, 180]. Bellgrove et al. [15, 16] reported an association between the A2 allele of the TaqI *DBH* polymorphism and impaired temporal resolution and sustained attention, with those homozygous for the A2 allele performing worse than those without this genotype. Barkley et al. [12] found the A2 allele to be associated with poor performance on a card playing task in adulthood and, when for individuals homozygous for A2, in adolescence. Kieling et al. [82] reported an association between a different polymorphism of *DBH*—the −1021C>T polymorphism, which may account for up to 50% reduction of the enzymatic activity—and measures of executive functioning in 64 drug-naive patients with ADHD. Cognitive performance measured by a composite score was significantly different between genotype groups, with the CC homozygous carriers having a poorer global executive performance. In contrast, Hess et al. [75] detected no association between the −1021C>T polymorphism and ADHD, but suggested that the marker may be related to impulsive personality traits in an adult ADHD sample. Finally, the re-analysis of the IMAGE GWAS data revealed a nominally significant association finding at the *DBH* locus and ADHD [95]; the same finding was also described in a Chinese Han population [65].

A recent meta-analysis of studies investigating the association between the Val/Met polymorphism of the catechol-o-methyltransferase (*COMT*) gene at codon 158 and ADHD concluded that the current evidence does not support an association with the disorder [29]. This conclusion is supported by results from the IMAGE project on

this polymorphism [21]. Subsequent studies have reported both association [47, 94, 95], no association [160] or a more complicated mode of action. Halleland and co-workers identified a haplotype including the Val158Met polymorphism associated with adult ADHD [68]. A study by Sengupta et al. [155] showed that the Val/Met polymorphism modulates task-oriented behaviour, but it does not modulate the response of this behaviour to MPH treatment. Moreover, a study by Retz et al. [140] reported that a specific haplotype combination of *COMT* variants and variants of the noradrenaline transporter gene (*NET/SLC6A2*, see below) may be related to low ADHD scores. Furthermore, a report by Thapar et al. [171] suggests that the Val158Met variation in the *COMT* gene previously associated with altered executive functioning is actually associated with antisocial behaviour in ADHD, rather than with ADHD itself. Caspi et al. [28] reported similar findings showing that homozygous valine carriers at codon 158 of the *COMT* gene were more aggressive than those with the other two genotypes. Consequently, other studies focused on the relationship between *COMT* genotypes and ADHD comorbid disorders, such as conduct disorder (CD) and oppositional defiant disorder (ODD). Monuteaux et al. [125] did not detect an association between SNPs in the *COMT* gene and the risk for CD in an ADHD sample, whereas Qian et al. [136] reported on an association of the Val/Met variant with ADHD and comorbid ODD in a Chinese sample.

A number of studies have reported on additional dopaminergic genes. A potential involvement of the *MAOA* gene in ADHD was reported [35, 65, 149, 189] even though these positive findings were inconsistent regarding the risk alleles [120, 180]. Moreover, others failed to find association [114, 136]. While it may still be possible that variations in the *MAOA* gene are associated with persistence of ADHD into adolescence [100] and play a role in the variation in neuropsychological performance [149], Thapar et al. [172] suggested that variation in *MAOA* is associated with antisocial behaviour in ADHD, but not with ADHD itself. Gender is a further factor that could mask effects of the gene on ADHD, Rommelse et al. [149], Das et al. [35] and recently Biederman et al. [19] reported gender differences in the association between gene variation and ADHD traits and suggested that the *MAOA* gene may explain some of the known gender differences in ADHD. As a possible mode of action, Rommelse et al. [149] described that an ATT haplotype of *MAOA* was associated with poor motor control in boys whereas it was associated with better visuo-spatial working memory in girls. Besides the *MAOA* gene, there are also reports on variants of the *MAOB* gene that were described to be associated with adult ADHD in a Spanish sample [143] and two additional studies [101, 143].

Noradrenergic system

While stimulant medications appear to act primarily by regulating dopamine levels in the brain, noradrenergic and serotonergic functions may also be affected by ADHD medications [159]. In addition, adrenergic neurotransmitter systems are hypothesized to influence attentional processes and certain aspects of executive control [4]. The most frequently investigated genes of the noradrenergic system are those encoding the noradrenaline transporter (*NET1/SLC6A2*) and the adrenergic alpha receptors 2A and 2C (*ADRA2A* and *ADRA2C*). Additionally, there is some evidence for a potential involvement of the genes for alpha receptors-1A and 1B (encoded by *ADRA1A* and *ADRA2B*) and beta receptor 1 and 2 (*ADRB1* and *ADRB2*) in the aetiology of ADHD [95].

An initial positive finding for the noradrenaline transporter (*NET1/SLC6A2*) [34] was followed by several studies that found no association [13, 30, 119]. Recently, several additional variants of the noradrenaline transporter have been associated to ADHD [20, 22, 65, 83, 84, 86, 95, 191, 192] and require further attention and more elaborate analyses. One example of such an analysis was already described above, suggesting that variations in the noradrenaline transporter may show effects in the presence of specific variants in the *COMT* gene (and vice versa), only [140]. Additionally, two studies also suggested gender-specific effects: Biederman et al. [19] found variants in *NET1/SLC6A2* to be associated more strongly with ADHD in females, whereas Anney et al. [2] reported about paternal over transmission of risk alleles to affected individuals.

Regarding other candidate genes of the noradrenergic system, there is growing evidence for involvement of genetic variants of the adrenergic receptor alpha-2A gene (*ADRA2A*) in ADHD [2, 30, 39, 145, 152, 184]. It may be that these variants are more relevant for inattentive than hyperactive/impulsive symptoms [145, 152]. Also it has been suggested that there is a relationship between *ADRA2A* polymorphisms and neuropsychological functioning that may moderate but not mediate the association to ADHD [181].

Investigating another adrenergic receptor gene, Cho et al. [31] reported associations between variants of the alpha-2C adrenergic receptor gene (*ADRA2C*) and ADHD in their sample of Korean subjects. They found that homozygous carriers of the C allele of the *Dral* polymorphism in *ADRA2C* showed a trend towards increased response time variability while individuals homozygous for the G allele at the *Mspl* polymorphism had a trend towards decreased response time variability. Guan et al. [65] reported suggestive significance for an association of *ADRA2C* variants with ADHD combined type.

Finally, the alpha-1A adrenergic receptor gene (*ADRA1A*) and the beta-2 adrenergic receptor gene (*ADRB2*) were two of the genes with nominal significance in the study of Brookes et al. [21] that were also identified by Lasky-Su et al. [95]. Very recently, Elia et al. [47] also described a potential association between *ADRA1A* and ADHD.

Serotonergic system

Serotonin dysregulation has been related to impulsive behaviour in children [69], and thus has been hypothesized to play a causal role in ADHD [129]. "Knockout" gene studies in mice, in which the behavioural effects of the deactivation of specific genes are examined, have further demonstrated the potential relevance of serotonergic genes [60]. The main candidate genes studied within the serotonergic system are those coding for the serotonin transporter (*5-HTT/SLC6A4*), the 1B and 2A serotonin receptors (*HTR1B*) and (*HTR2A*) and the dopamine decarboxylase (*DDC*) and tryptophan hydroxylase (*TPH2*) genes. Several other serotonin receptor genes have also been studied much less extensively.

A meta-analysis has supported an association between ADHD and a 44-base-pair insertion/deletion (5-HTTLPR) in the promoter region of the serotonin transporter gene (*5-HTT/SLC6A4*); this insertion/deletion causes long or short alleles with the long variant coding a functionally more active transporter which may contribute to the ADHD association (pooled odds ratio ~1.3) [53]. However, although there have been further replications since this meta-analysis [89, 104, 139] several studies have failed to replicate this finding [21, 64, 120, 187, 188] while still others have found the other allele to be associated [1, 104]. Moreover, there have also been reports that the association of 5-HTTLPR may only be present when paired with an intron-2 (STin2) polymorphism [11] and that the intron-2 (STin2) polymorphism itself may be the variant more relevant for ADHD.

There are also contradictory findings for the potential association of the serotonin receptors with ADHD. A meta-analysis supported an association between the *HTR1B* gene and ADHD (pooled odds ratio ~1.44; [53]), and although there are subsequent additional replications for *HTR1B* [70, 137], there are again also negative findings [21, 77]. Similarly, several groups have reported positive findings for *HTR2A* [67, 143], whilst others have failed to find an association [40, 146]. An analysis of the IMAGE study reported an association with the previously unstudied *HTR1E* gene but did not find an association to *HTR2C* or *HTR3B* [95]. Isolated findings in Chinese Han subjects and others have been reported for several other serotonin receptor genes including those coding for *HTR1D* [108, 109], *HTR2C* [106, 190] and *HTR4* [102] but not others *HTR5A* and *HTR6* [103]. Li et al. [99] also reported that polymorphisms of the *HTR2A* and *HTR2C* genes are related to functional remission in ADHD.

Li and colleagues have also reported on ADHD associations for the tryptophan hydroxylase 2 gene (*TPH2*) which mediates the transformation of tryptophan to 5-hydroxytryptophan [105, 107]. These findings have been replicated in independent samples [21, 95, 157, 182]. Moreover, an analysis of the IMAGE data revealed nominal significance for an association between *TPH2* variants and overt aggressive impulsivity [130]. Baehne et al. [8] reported that *TPH2* gene variants modulate response control processes in adult ADHD patients and healthy individuals. Regarding tryptophan hydroxylase 1 (*TPH1*), no ADHD association was found in the IMAGE sample [21]. Finally, Ribases et al. [143] reported that the *DDC* gene, which mediates the transformation of 5-hydroxytryptophan to serotonin, is associated to both adult and childhood ADHD.

Other candidate genes

Additional candidate genes that have been studied include genes related to the following non-exhaustive list of gene products: Synaptosome-associated protein of 25,000 Da (*SNAP25*), nicotinic acetylcholine receptor alpha 4 (*CHRNA4*), the glutamate (*NMDA*) receptor, brain derived neurotrophic factor (*BDNF*), nerve growth factor (*NGF*) and its receptor (*NGFR*), neurotrophins 3 and 4/5 (*NTF3* and *NTF4/5*), ciliary neurotrophic factor (*CNTF*) and its receptor (*CNTFR*), glial derived neurotrophic factor (*GDNF*) and the receptors for neurotrophic tyrosine kinase, type 1–3 (*NTRK1, NTRK2* and *NTRK3*), low affinity nerve growth factor receptor (*LNGFR* or *p75* neurotrophin receptor), solute carrier family member 9A9 (*SLC9A9*), cannabinoid receptor 1 (*CNR1/CB1*) and nitric oxide synthase 1 (*NOS1*) [21, 95].

For *SNAP25*, meta-analyses of studies indicated significance of association findings for ADHD [52], for *SLC9A9* also cytogenetic findings point to a role in ADHD [38], and for the functional Val66Met variant of *BDNF*, a very recent meta-analysis of the IMpACT project data showed no association with ADHD with or without comorbid mood disorders, in a large clinical sample of clinical adult ADHD cases ($n = 1{,}445$) and controls ($n = 2{,}247$) [151]. For the other genes mentioned above the results of the association analyses are either first reports based on samples of small or moderate size or where there is more than one report with contradictory findings. Obviously, contradictory results can arise for many reasons, but inadequate power to

detect associations with small effect sizes and inexplicit analysis plans with multiple post hoc comparisons are the most common and obvious problems. To address this issue, carefully planned meta-analyses on studies with adequate quality or primary studies of sufficient size are needed.

Genome-wide association studies in ADHD

Genome-wide association studies have been a very successful tool for the recent identification of multiple risk genes for multifactorial (complex) disorders [116]. They combine the power to detect genetic variants of small effect size, like the association studies, with the possibility to perform hypothesis-free analyses of the entire genome. However, large sample sizes are needed in order to detect genetic risk factors with modest effects. So far, GWAS in ADHD have been published for two different samples, a subsample of the International Multicentre ADHD Genetics (IMAGE) study on childhood ADHD and a sample of adults with ADHD. These studies will be reviewed below. For a more detailed review see also [56].

The various GWAS analyses of the IMAGE sample that were published together in a special issue on ADHD genetics in the Am. J. Med. Genet. Part B (2008), used different approaches to identify risk genes. The IMAGE GWAS sample comprised a sample of 958 case-parent trio's with most of the cases diagnosed with combined subtype ADHD. The data were analysed using both quantitative [95] and categorical [127] phenotype definitions. The quantitative analysis revealed two significant findings: one for a genetic variant in the *CDH13* gene associated with total ADHD symptom count, the other for a genetic variant in *GFOD1*, the gene coding for glucose-fructose oxidoreductase domain containing protein 1, associated with inattentive symptoms. Another interesting finding from this study (though not statistically significant) included a variant in *NOS1*, which had previously been identified as a candidate gene for ADHD [138]. The categorical analysis did not reveal any genes or variants of genome-wide significance, but *CDH13* was also among the top-findings identified in this analysis, as was a variant in *CNR1*/*CB1*, a gene found associated with ADHD in earlier candidate gene based association studies [113, 133].

A whole genome gene-environment interaction study of parental expressed emotion (maternal warmth and criticism) looking at ADHD severity (and conduct problems) was also conducted using the same dataset, although there were again no genome-wide significant findings [162]. Additional GWAS in the IMAGE dataset so far included a study of time of onset of hyperactive/impulsive and inattentive symptoms [94] and one on conduct problems in ADHD [2].

The GWAS of adult ADHD patients used a pooled approach involving 343 adult ADHD patients and 304 controls [96]. The results of this study were compared to those of a linkage analysis carried out earlier by the same group [146] to prioritize the most interesting findings for further analysis. Although no genome-wide significant variants resulted from this study, the highest ranking findings also include the *CDH13* gene. This gene emerges hitherto as one of the most consistent findings from the ADHD GWAS. In addition, it is supported by other sources, e.g. being located on chromosome 16q24 within the only significant linkage peak from a meta-analysis of seven linkage studies in ADHD [196]. Since *CDH13* also showed association with different addiction-related phenotypes in GWAS (review by Uhl et al. [175]), was among the top-findings from a GWAS of the personality trait extraversion [170], showed strong association with schizophrenia in a genome-wide study [164], and may contain copy number variants (CNV) related to autism [32], it seems to be a generalist gene, predisposing to multiple brain phenotypes [90]. *CDH13* encodes cadherin 13, a protein expressed in neurons regulating cell migration and cell–cell communication [56].

Although only very few significant findings emerged from the individual ADHD GWAS, so far, and overlap between studies is still very limited, there are a few systems that seem to be overrepresented in the top-ranks of the different studies and a number of general themes seem to be emerging from the data. The most striking one is the possible involvement of genes related to cell adhesion and cell migration in ADHD aetiology, such as genes from cadherin, catenin and integrin families (Table 1), with *CDH13* as the top-finding.

A second system showing up in these studies is that of potassium-related signalling (Table 2). This type of signalling is involved in regulating synaptic excitability and neuronal plasticity [85]. An interesting finding from the GWAS is that whilst signals relating to cell–cell communication genes related to glutamate, vasopressin and TAFA mediated signalling are observed the classical catecholaminergic and serotonergic neurotransmission ADHD candidate genes are absent from the high-ranking findings. However, since the power of these studies is still rather limited, the involvement of the genes for the classical neurotransmission systems in ADHD aetiology is not precluded.

Notably, nearly all of the genes listed in the top-ranks of the published ADHD GWAS belong to the largest genes within the human genome (Franke, unpublished observation), which may also point to insufficient power of the studies to detect association with smaller genes. As indicated above, some of the genes from candidate gene studies do show up in the GWAS, most notably *CNR1* and *NOS1*.

Table 1 Genes encoding proteins involved in cell adhesion and migration (GWAS findings)

SNP	*P* value	Chr	Position (bp)	Position	Gene function[a]	Additional remarks
rs7187223	5.21E−05[c]	16	81015234	Intergenic, within 203 kb upstream from CDH13	Encodes cadherin 13, a member of the cadherin superfamily. The encoded protein is a calcium dependent cell–cell adhesion glycoprotein. This particular cadherin is a putative mediator of cell–cell interaction in the heart and may act as a negative regulator of neural cell growth. Lies within the only significant linkage region for ADHD as determined in meta-analysis [196]. Has earlier shown association with metamphetamine dependence in GWAS [176] as well as multiple other addiction related phenotypes [175]. Gene is also found in GWAS in schizophrenia with p values at 10^{-4} [164] and shows CNVs potentially related to autism [32]	Neale et al. [127]. Also shows association with adult ADHD in the GWAS by Lesch et al. [96]
rs11646411	7.40E−06**	16	81304438	In intron of CDH13	See above	Lesch et al. [96]
rs6565113	n.a.[b]	16	81665146	Intron of CDH13	See above	Associated with total symptom count, Lasky-Su et al. [95]
rs930421	5.64E−06[d]	2	42834743	Exon of MTA3	Encodes metastasis associated 1 family, member 3, a component of the nucleosome-remodeling and histone–deacetylase multiprotein complex (NuRD). MTA3 plays a role in maintenance of the normal epithelial architecture through the repression of SNAI1 transcription in a histone deacetylase-dependent manner, and the regulation of E-cadherin levels. Expressed in multiple tissues, including brain, especially cerebellum	Associated with total symptoms, Lasky-Su et al. [95]
rs6719977	1.67E−06[d]	2	42839307	Within 2 kb downstream of MTA3	See above	Associated with hyperactive/impulsive symptoms, Lasky-Sue et al. [95]
rs17079773	4.71E-06[d]	13	23496384	In intron of SPATA13	Encodes spermatogenesis associated 13, potentially involved in cell migration. Expressed in brain	Associated with inattentive symptoms, Lasky-Su et al. [95] Site known for CNVs
rs16928529	3.90E−06**	10	72652991	In intron of UNC5B	Encodes unc-5 homolog B (*C. elegans*), which belongs to a family of netrin-1 receptors thought to mediate the chemorepulsive effect of netrin-1 on specific axons. Finding lies in linkage region for bipolar disorder [128]	Lesch et al. [96]
rs10983238	1.37E−07**	9	118373504	In intron of ASTN2	Encodes astrotactin 2, a membrane protein expressed in multiple tissues including brain. It is critically involved in neuron-glia binding during the developmental periods of glial-guided cell migration and assembly into neuronal layers in the developing brain [96]. A homologue of the gene, ASTN, is involved in neuronal migration [178]. The gene was found disrupted by rare CNVs in schizophrenia patients [178] and patients with autism [118] shows association in GWAS of multiple addiction-related traits [175], as well as of schizophrenia [164]	Lesch et al. [96]. Also lies within suggestive linkage region for ADHD reported in the same publication (Lesch et al. [96]). Association also observed in the 50 K GWAS in the same publication. Three SNPs in the gene are among the highest-ranking 260 in the analysis

Table 1 continued

SNP	*P* value	Chr	Position (bp)	Position	Gene function[a]	Additional remarks
rs2281597	5.41E−07**	1	34132445	In intron of CSMD2	Encodes CUB and Sushi multiple domains 2, a protein with a potential role in cell adhesion and neurogenesis. Intermediate expression in fetal brain, adult brain, spinal cord, and all specific adult brain regions examined. Lower levels were detected in spleen, lung, and testis, and little to no expression was detected in the other tissues examined. The protein product is enriched in axonal growth cones and is involved in neuronal outgrowth during formation of neuronal circuits [96]. CSMD2 and its homologue CSMD1 have been found associated with addiction related phenotypes in multiple GWAS [175]	Lesch et al. [96]
rs220470	1.34E−07**	17	3611724	In intron of ITGAE	Encodes integrin alpha E. Integrins are heterodimeric integral membrane proteins composed of an alpha chain and a beta chain. Expressed in multiple tissues including brain. Finding lies within linkage region for ADHD from meta-analysis [196]	Lesch et al. [96] Also lies within suggestive linkage region for ADHD reported in the same publication (Lesch et al. [96])
rs7164335	1.30E−07**	15	66502086	In intron of ITGA11	Encodes integrin alpha 11. Integrins are heterodimeric integral membrane proteins composed of an alpha chain and a beta chain. Expressed in multiple tissues including brain. The finding lies close to linkage regions for autism [168]	Lesch et al. [96]. Site known for CNVs
rs11594082	1.00E−05**	10	72969259	In intron of CDH23	Encodes cadherin-like 23, a member of the cadherin superfamily, whose genes encode calcium dependent cell–cell adhesion glycoproteins. Expressed in the neurosensory epithelium, the protein is thought to be involved in stereocilia organization and hair bundle formation; also expressed in brain. The gene is involved in deafness. Finding lies close to linkage region for bipolar disorder [128]. Gene shows association with schizophrenia at p values of 10^{-4} [164]	Lesch et al. [96]
rs7995215	1.35E−08**	13	93206507	In intron of GPC6	Encodes glypican 6. The glypicans comprise a family of glycosylphosphatidylinositol-anchored heparan sulfate proteoglycans. The glypicans have been implicated in the control of cell growth and division. Glypican 6 is a putative cell surface coreceptor for growth factors, extracellular matrix proteins, proteases and anti-proteases. Expressed in multiple tissues including brain. SNPs in the close vicinity of this finding showed association at 10^{-4} in GWAS for bipolar disorder [158]. Gene shows association with schizophrenia [164] and bipolar disorder [158] at $p = 10^{-4}$ and CNVs in the gene have been noted in a study on autism [118]	Lesch et al. [96]
rs13395022	9.68E−06**	2	79735768	In intron of CTNNA2	Encodes catenin alpha 2, expressed in brain and other tissues. The activity of cadherins, which mediate homophilic cell–cell $Ca^{(2+)}$-dependent association, depends on their anchorage to cytoskeleton via catenins. Catenin alpha 2 functions as a critical agent to regulate the stability of synaptic contacts. Cell-adhesion complexes of catenin alpha 2 with cadherin are likely most important in cerebellar and hippocampal lamination. Finding lies within a linkage region for schizophrenia from meta-analysis [97]. Gene shows association with schizophrenia [164] at p values of 10^{-5} and bipolar disorder [185] at $p = 10^{-4}$	Lesch et al. [96]. Gene also shows association with ADHD at $p = 10^{-4}$ in GWAS of Neale et al. [127]

Table 1 continued

SNP	*P* value	Chr	Position (bp)	Position	Gene function[a]	Additional remarks
rs874426	3.75E−06[d]	11	19526139	In intron of NAV2	Encodes neuron navigator 2, an retinoic acid-responsive gene that seems to play a role in neuronal development. It is highly expressed in fetal and adult brain. Lies within/close to linkage region for autism from primary studies and meta-analysis [46, 168, 173]. Gene is associated with bipolar disorder in GWAS at p values of 10^{-4} [158]	Associated with an earlier onset of ADHD symptoms in Lasky-Su et al. [94]. Also associated with ADHD at $p = 10^{-4}$ in GWAS of Neale et al. [127]

[a] Where not indicated otherwise, the information is derived from the UCSC Browser, NCBI's OMIM, Gene and Unigene databases, and the Sullivan Lab Evidence Project website (location of SNP expanded by ±5 mb for genome-wide linkage scans, ±5 kb for GWAS, microarray and CNV studies, and ±50 kb for signposts)

[b] These findings were derived using the PBAT screening procedure prior to association testing

[c] TDT analysis

[d] FBAT analysis

** ANOVA p value for ranking

Also more basic cell processes related to cell division, gene transcription, cell polarity and extracellular matrix regulation, as well as cytoskeletal remodeling could be involved in ADHD [95, 96, 127]; see [56] for a review.

Whilst the current GWAS published for ADHD are far from providing a full understanding of the processes contributing to ADHD, they do provide us with new directions and suggest avenues follow. Comparing the findings to those from GWAS and linkage studies in other psychiatric disorders suggests extensive overlap between disorders. If this is due to overlap at the level of diagnostics or to genetic overlap between disorders remains to be explored.

Future directions in ADHD genetics research

To date, the findings from genetic studies in ADHD have been somewhat inconsistent and disappointing. Despite the high heritability of the disorder, linkage studies have not shown extensive overlaps, with only one significant finding in the meta-analysis of studies [196]. Candidate gene based association studies have similarly only explained a small percentage of the genetic component of ADHD and the first GWAS did not report many significant findings. Nevertheless, the latter approach is likely to redirect future ADHD research given the apparent involvement of new gene systems and processes, as summarized above.

Comparing GWAS in psychiatric disorders in general with those in other multifactorial diseases one finds that the performance of GWAS in psychiatric disorders has been particularly poor, explaining less than 10% of the observed variance for most of the disorders, so far [115]. The failure of the GWAS to identify the genes involved in psychiatric disorders with high heritability may have a number of causes: (1) multiple genetic factors may be involved that may have very small individual effects and might only be identified through studies with extremely large sample sizes; (2) gene–gene (G × G) and gene-environment (G × E) interactions may be making a strong contribution to the observed heritability of psychiatric disorders; (3) genetic factors other than the single nucleotide polymorphisms (SNPs) investigated in most studies may play important roles; thus, CNVs, i.e., structural variations in DNA, such as insertions, deletions and duplications, which are frequently occurring but widely varying in the population, might be involved in ADHD aetiology; (4) the role of rare genetic variants with large effect sizes in disease aetiology may be greater than anticipated; (5) the currently available nosological systems used for the clinical diagnosis of psychiatric disorders may be clinically valid but may not be strongly related to the biological underpinnings of such disorders, or may not be specific enough to pick up genes; and (6) it

Table 2 Genes encoding proteins related to potassium-mediated signalling (GWAS findings)

SNP	*P* value	Chr	Position (bp)	Position	Gene function[a]	Additional remarks
rs876477	2.69E−05[b]	4	20766026	Intron of KCNIP4	Encodes Kv channel interacting protein 4 isoform 3, a member of the family of voltage-gated potassium (Kv) channel-interacting proteins (KCNIPs), and may regulate A-type currents, and hence neuronal excitability, in response to changes in intracellular calcium. The KCNIP4 protein also interacts with presenilin. Gene is also found among top-findings from GWAS in schizophrenia [164] and shows p values of 10^{-5} in GWAS in bipolar disorder [158]	Neale et al. [127]. Also shows nominal association ($p < 0.05$) in quantitative GWAS by Lasky-Su et al. [95]
rs1541665	5.60E−05[b]	5	170075495	Intron of KCNIP1	Encodes Kv channel interacting protein 1 isoform 2, a member of the family of voltage-gated potassium (Kv) channel-interacting proteins (KCNIPs), and may regulate A-type currents, and hence neuronal excitability, in response to changes in intracellular calcium. Lies close to linkage region observed in several primary studies as well as a meta-analysis [97]. Gene is also found in GWAS in schizophrenia with p values of 10^{-4} [164]	Neale et al. [127]. Also shows nominal association ($p < 0.05$) in quantitative GWAS by Lasky-Su et al. [95]
rs272000	9.10E−06[c]	2	116372265	Within 50 kb downstream of DPP10	Encodes dipeptyl peptidase 10, which does not possess dipeptidyl peptidase activity but binds to specific voltage-gated potassium channels and alters their expression and biophysical properties. The expression of the gene is highest in brain. The finding lies within a linkage region for schizophrenia observed in meta-analysis and several primary studies [97]. In addition, the gene showed association in GWAS of schizophrenia [164] and bipolar disorder [185] at $p = 10^{-5}$, and contains CNVs potentially linked to autism [118]	Associated with total symptom count, Lasky-Su et al. [95]. Site known for CNVs
rs6791644	8.32E−06[c]	3	60746148	In intron of FHIT	Encodes a diadenosine 5′,5‴-P1,P3-triphosphate hydrolase involved in purine metabolism. FHIT has a major role in regulating beta-catenin-mediated gene transcription. Expression in many tissues including brain. Gene is also found among top-findings from GWAS in schizophrenia [164] and is affected by CNVs in autism [118, 154]	Associated with total symptom count, Lasky-Su et al. [95]
rs3893215	2.56E−05**	11	17721406	In intron of KCNC1	Encodes potassium voltage-gated channel Shaw-related subfamily member 1, a protein belonging to the delayed rectifier class of channel proteins and an integral membrane protein that mediates the voltage-dependent potassium ion permeability of excitable membranes. The finding is present close to/within regions of (suggestive) linkage to autism from meta-analysis [173] and primary studies [46, 167]	Lesch et al. [96]

[a] Where not indicated otherwise, the information is derived from the UCSC Browser, NCBI's OMIM, Gene and Unigene databases, and the Sullivan Lab Evidence Project website (location of SNP expanded by ±5 mb for genome-wide linkage scans, ±5 kb for GWAS, microarray and CNV studies, and ±50 kb for signposts)

[b] TDT analysis

[c] FBAT analysis

** ANOVA p value for ranking

must be kept in mind, that the samples studied differ in age (persistent vs. non-persistent ADHD), method of recruitment and ascertainment, ethnicity, gender and comorbidity and that each of these factors might have an impact. These issues need to be dealt with, before we can fully understand the genetic architecture of ADHD. The issue of sample size is currently tackled by establishing large international collaborations, such as the ADHD Molecular Genetics Network [49] and the Psychiatric GWAS Consortium [134], and large (meta-analytic) studies of GWAS in ADHD can be expected within the next year. The G × G and G × E effects are not yet taken into account in most current studies, but some potentially important G × G and G × E interactions have been demonstrated. It is likely that new statistical approaches will need to be developed, before we can sufficiently handle these effects with confidence. Until now, most studies have focussed on SNPs only, however, this type of polymorphism is not informative for all genetic factors present in the human genome, and we might need to use other techniques, such as next generation sequencing [153] to get more information on these other genetic factors. This approach may also solve the problem with rare variants. Point (5), the potential limitations through the use of the current diagnostic system for genetic studies, can potentially be addressed by using more refined phenotypes. Refinement of the ADHD phenotype may be possible by concentrating on the most heritable subtypes of ADHD. This has already been implemented in the IMAGE study, which concentrated on combined subtype ADHD [91]. Recently, the IMpACT project was set up by research groups from The Netherlands, Germany, Spain, Norway, the UK and the US to perform and promote genetic research in the persistent, adult form of ADHD [57]. Although the heritability of this form of the disorder has not formally been established, it seems that it may be higher than that of the childhood disorder [48]. To date, IMpACT coordinates the largest clinical sample of adult ADHD, with more than 2,700 cases and 3,500 controls. A more radical adaptation in phenotypes for genetic studies in ADHD is the use of endophenotypes. Endophenotypes, or intermediate phenotypes, are thought to represent heritable phenotypic constructs that are more directly related to genes than clinical symptoms or disease categories [63, 169, 183]. The success of an endophenotype strategy requires either a higher heritability of the endophenotype as compared to the disease phenotype (which is not generally observed, [167]) or a reduced complexity of the genetic architecture of the endophenotype due to the involvement of fewer genes. ADHD endophenotypes have been identified at different levels, based on neuropsychological performance [41, 147] and on neuroimaging [43] i.e. brain activity and structure. Such studies seem to work well, the first examples of linkage studies show significant findings in samples of relatively limited size (e.g. [42, 150]) and so do (candidate gene based) association findings (e.g. references to Durston et al. [45]). Especially the latter seem to produce more highly powered studies due to larger effect sizes of individual genetic variants [121, 126]. The penetrance of genetic variants may be especially high for functional neuroimaging [121]). However, it needs to be taken into account that initial studies of genetic associations frequently tend to over-estimate true effect sizes [174]; thus, we need to be cautious about interpretation of the initial studies of endophenotypes in relatively small sample sizes.

Endophenotype approaches come at the cost of reduced specificity for ADHD, so not all genes explaining variance of an endophenotype will also increase ADHD risk in the end; however, it is not yet clear whether factors such as course or treatment response are more closely related to ADHD per se or to a particular endophenotype.

Furthermore, endophenotype studies will also help to characterize the neural systems affected by risk gene variants and to elucidate quantitative, mechanistic aspects of brain function implicated in ADHD, and thus improve our understanding of the functional role of genes in ADHD and the specific pathways from gene to behaviour.

In conclusion, genetic studies have started to unravel the molecular architecture of ADHD, and several new exciting directions have recently been suggested. Future success in identifying more ADHD genes will critically depend on collaboration between researchers and an improvement of approaches at the level of the phenotype definition, the molecular genetic techniques, as well as statistical analysis methods. Even if the ADHD risk genes have such small effect sizes in the population, their identification may still be highly relevant clinically, because low frequency gene variants may actually explain most of the heritability in individual patients and because a subsequent understanding of their functions and the pathways between each gene and behaviour may finally translate into an improvement of diagnostic processes and treatment strategies as well as a development of prediction and prevention programs with substantial impact [132].

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