ADHD: strategies to unravel its genetic architecture

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Summary. Attention deficit/hyperactivity disorder (ADHD) is a common and impairing neuropsychiatric disorder with onset at preschool age and strong persistence over time. Its validity as a psychiatric disorder has been established according to Robins and Guze criteria. Genetic factors predominate in the etiology of ADHD. This paper summarizes the current status of genetic research into ADHD, and describes eight factors that complicate research into genetically complex disorders as ADHD. These factors are that multiple genes of small main effects are involved rather than main genes, the relevant phenotype is unknown, presence of clinical heterogeneity, presence of genetic heterogeneity, gene-environment correlation, gene-environment interaction, importance of endophenotypes, and importance of developmental factors. The further unraveling of the genetic architecture of ADHD will depend to a large extent on how well these complicating factors are handled or even used.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common and impairing neuropsychiatric disorder with onset at preschool age. It is thought to affect 3–5% of all schoolage children and is characterized by age-inappropriate symptoms of hyperactivity, inattentiveness and impulsivity (American Psychiatric Association, 1994; Buitelaar, 2002). This pattern can be viewed as the extreme of a complex trait that is continuously distributed in the general population and shows a strong overlap with aggressive behavior. The Fourth Edition of the Diagnostic and Statistical Manual (DSM-IV) recognizes three subtypes of ADHD, the predominantly inattentive subtype, the predominantly hyperactive-impulsive subtype and the combined subtype (American Psychiatric Association, 1994). Eighty percent of the children that are diagnosed with ADHD display symptoms in all three domains of inattentiveness, hyperactivity and impulsivity, though at the level of the general population, the inattentive subtype of ADHD is most prevalent (Buitelaar, 2002). There is a much higher incidence rate in boys, who are 1.5–5.8 times more likely than girls to be diagnosed with ADHD (Buitelaar, 2002). The disorder often has a chronic course with about 70% of affected children having threshold ADHD symptoms and associated impairment in

adolescence and 30–50% of affected children displaying ADHD symptoms into adulthood (Weiss et al., 1993; Barkley et al., 1990). The presence of comorbid disorders is the rule rather than the exception. Common comorbidities in children and adolescents include oppositional defiant disorder and conduct disorder, anxiety disorders, mood disorders (Biederman et al., 1991), tic disorders, motor coordination disorder (Robinson et al., 1993), learning disabilities (Semrud-Clikeman et al., 1992) and problems in reciprocal social interaction and communication that overlap with those described in autism spectrum disorders (Luteijn et al., 2000a, b). In adolescence and adulthood, comorbid risk taking behaviors and substance abuse disorders are rising in prevalence (Wilens, 2004) as well as antisocial personality disorder (Mannuzza et al., 1989) and borderline personality disorder (Fossati et al., 2002). Numerous problems are further associated over development with ADHD, such as poor academic performance, school drop out, social isolation, and lower occupational success (Weiss et al., 1993; Barkley et al., 1990).

ADHD has been firmly established as a psychiatric disorder that meets the criteria for the validation of psychiatric diagnoses as outlined by Robins and Guze (1970) (Faraone, 2005a). In spite of this, the disorder's validity has been challenged and criticized by popular media, journalists and politicians (Buitelaar and Rothenberger, 2004). ADHD has been stated to be a result of inadequate parenting and teaching in an overstressed society which places too high demands on children's self-control and self-organizational skills. Normal developmental variation and particularly boyish energy and adventurousness have been medicalized. Worries have been further expressed about potential overdiagnosis and overtreatment of ADHD, and particularly on the dangers of the treatment with psychostimulants. Unfortunately, this has led to increased barriers for referral and block access to adequate diagnosis and treatment for children with ADHD and their parents (Buitelaar and Rothenberger, 2004).

The aim of this communication is to summarize the current status of genetic research into ADHD and to describe strategies to further unravel ADHD's genetic architecture.

Behavior-genetic studies

Twin, family, adoption and molecular genetic studies show that genes play a very substantial role in the etiology of ADHD. Family-genetic studies indicate that ADHD aggregates in families, with a 5–8 fold increased risk in first-degree relatives and a 2-fold increased risk in second-degree relatives (Faraone et al., 1994). Twin studies found evidence for a narrow additive heritability of 0.75 to 0.91 which was robust across familial relationships and across definitions of ADHD as the end of a continuum or as a disorder with various symptom cutoffs (Levy et al., 1997; Sherman et al., 1997). For further review of twin studies, see Faraone et al. (2001) and Thapar et al. (1999). Given the modest relative risk ratios in siblings and the fall-off in risk from first to second-degree relatives, the high heritability of ADHD is likely to be due to multiple genes of small effect size (called quantitative trait loci, QTLs, or susceptibility genes) rather than a few genes of major effect. The latter result of the twin studies further indicates

that a QTL approach to the study of the genetics of ADHD is valid and that genes associated with a complex trait measure of ADHD very likely will also show to be relevant for ADHD defined as a categorical psychiatric disorder, and vice versa. The fact that heritability is less than 1.0 shows further that features of the environment are also involved in the etiology of the disorder.

Adoption studies of ADHD also implicate genes in its etiology. The adoptive relatives of ADHD children are less likely to have ADHD or associated disorders than are the biological relatives of ADHD children (Morrison et al., 1973; Cantwell, 1975). Biological relatives of ADHD children also do more poorly on standardized measures of attention than do adoptive relatives of ADHD children (Alberts-Corush et al., 1986).

Genome scans

To date, there have been performed three independent genome scans of ADHD. Table 1 summarizes their main results. A first genomewide scan for loci involved in ADHD in 126 affected sib pairs pointed to a number of chromosomal sites that may contain risk factors of moderate effect (Fisher et al., 2002). None of these exceeded genomewide significance thresholds, with LOD scores >1.5 (but <1.66) on 5p12, 10q26, 12q23 and 16p13. The regions containing 29 out of 36 candidate genes, including DRD4 and DAT1, could be excluded for a λ of 2. An extension study in a larger sample of 227 ASPs that focused on chromosome 16q13 was able to establish linkage (LOD score 4.2) (Smalley et al., 2002). A further follow-up investigation extended the original sample of 126

Table 1. Summary of regions implicated in genome scans of ADHD and overlap with regions implicated in other disorders

Study	Region	LOD	Implicated in autism ⁴	Implicated in dyslexia ⁵
UCLA ¹	5p13	2.6	X	
UCLA ¹	6q12	3.3		
UCLA ¹	16p13	3.7	X	
UCLA ¹	17p11 [#]	3.6	X	
Netherlands ²	15q15	3.5	X	X
Netherlands ²	7p13	3.0		
Netherlands ²	9q33	2.1		
Columbia ³	17p11 [#]	2.8	X	
Columbia ³	11q22	2.5		
Columbia ³	5q33.3	2.4		

¹UCLA study of 270 sib-pairs (Fisher et al., 2002; Smalley et al., 2002; Ogdie et al., 2003, 2004)

²Dutch study of 164 sib-pairs (Bakker et al., 2003)

³Columbian study of 14 three-generation pedigrees (Arcos-Burgos et al., 2004)

⁴For review of genome scans in autism, see Muhle et al. (2004)

⁵For review of genome scans in dyslexia, see Demonet et al. (2004)

[#]Replication of same region

ASPs to 270 ASPs and provided linkage analyses of the entire sample (Ogdie et al., 2003). Maximum LOD score (MLS) analysis identified suggestive linkage for 17p11 and four nominal regions with MLS values 11.0, including 5p13, 6q14, 11q25, MLS p 2.98 and 20q13. These data, taken together with the fine mapping on 16p13, suggested two regions as highly likely to harbor risk genes for ADHD: 16p13 and 17p11. Next, fine mapping was completed of nine positional candidate regions for ADHD in an extended population sample of 308 ASPs (Ogdie et al., 2003). The candidate chromosomal regions were selected from all three published genomewide scans for ADHD, and fine mapping was done to comprehensively validate these positional candidate regions in our sample. Multipoint maximum LOD score (MLS) analysis yielded significant evidence of linkage on 6q12 (MLS 3.30) and 17p11 (MLS 3.63), as well as suggestive evidence on 5p13 (MLS 2.55).

A second genome scan was performed on 164 Dutch affected sib pairs (ASPs) with ADHD (Bakker et al., 2003). Initially, a narrow phenotype was defined, in which all the sib pairs met the full ADHD criteria (117 ASPs). In a broad phenotype, additional sib pairs were included, in which one child had an autistic-spectrum disorder but also met the full ADHD criteria (164 ASPs). This genome scan indicated several regions of interest, two of which showed suggestive evidence for linkage. The most promising chromosome region was located at 15q, with an MLS of 3.54 under the broad phenotype definition. This region was previously implicated in reading disability and autism. In addition, MLSs of 3.04 and 2.05 were found for chromosome regions 7p and 9q in the narrow phenotype. Except for a region on chromosome 5, no overlap was found with regions mentioned in the only other independent genome scan in ADHD reported to date.

The third genome scan was performed in 14 three-generation pedigrees with ADHD from a genetic isolate (Arcos-Burgos et al., 2004). In these families, ADHD is highly comorbid with conduct and oppositional defiant disorders, as well as with alcohol and tobacco dependence. Evidence was found of linkage to markers at chromosomes 4q13.2, 5q33.3, 8q11.23, 11q22, and 17p11 in individual families. Fine mapping applied to these regions resulted in significant linkage in the combined families at chromosomes 4q13, 5q33.3, 11q22 and 17p11. Additionally, suggestive linkage was found at chromosome 8q11.23. Several of these regions were novel (4q13.2, 5q33.3, and 8q11.23), whereas others replicated already-published loci (11q22 and 17p11).

The lack of replication across the studies completed so far adds to the earlier conclusion that genes of moderately large effect are unlikely to exist, and for this reason, further studies are needed to increase the power of available linkage data. Another important outcome of the genome scans is that there appears to be considerable overlap in regions of the genome that are implicated in ADHD, and those that are implicated in other conditions as autism and dyslexia (Table 1).

Candidate gene studies

Numerous candidate genes have been studied for their possible association with ADHD. For more extensive review, see Faraone et al. (2005b). These candidate genes have been chosen to be relevant for current neurobiological theories of ADHD. Many groups have examined associations between

ADHD and genes involved in dopaminergic neurotransmission, mainly because psychostimulants, among the most effective drugs used to treat ADHD, partly block the dopamine transporter (DAT1) function (Volkow et al., 2001; Buitelaar et al., 1995). Dopamine acts also as a agonist at dopaminergic receptor systems. Most studies of the dopamine transporter (DAT1-SLC6A3) gene in ADHD have examined a 10 repeat sequence in the 3' untranslated region. When family-based studies of this polymorphism were pooled, the odds ratio is small but significant (1.13, 95% CI 1.03–1.24), suggesting that SLC6A3 merits further investigation but that its effect is modest. One of the best studied candidate genes is the Dopamine D4 receptor (DRD4). Researchers have predominantly focused on a tandem repeat polymorphism in exon III of DRD4 because in vitro studies have shown that one variant (the 7-repeat allele) produces a blunted response to dopamine (Asghari et al., 1995; Van Tol et al., 1992). Despite some variation across studies, when data from analyses of the exon III polymorphism are pooled, the association with ADHD remains statistically significant (case-control odds ratio = 1.45 (95% CI 1.27–1.65); family based OR = 1.16 (95% CI 1.03–1.31). Although the functional implications of mutations in DRD5 are not well understood, there is some evidence for association with long-term potentiation in corticostriatal regions and with locomotion and prepulse inhibition (Manor et al., 2004). A recent analysis that combined 14 independent samples from family-based studies (Lowe et al., 2004) identified a significant association of the 148 bp allele with ADHD, (OR = 1.2; 95% CI 1.1–1.4). Dopamine Beta-Hydroxylase (DBH) is the primary enzyme responsible for conversion of dopamine to norepinephrine. When family-based studies of this gene are pooled, they jointly suggest a significant association between ADHD and the 5' Taq1 polymorphism (OR = 1.33, 95% CI 1.11–1.59).

The norepinephrine transporter (SLC6A2) has been examined in ADHD because drugs that block the norepinephrine transporter are efficacious in treating ADHD (Banaschewski et al., 2004). No evidence of association was found for these loci or the haplotypes comprising them in a study that examined SNPs in exon 9, intron 9 and intron 13 in 122 ADHD families and found (Barr et al., 2002). No association with intron 7 and intron 9 SNPs was seen in a study of Irish families (McEvoy et al., 2002), or with a restriction fragment length polymorphism in offspring of adults with ADHD (De Luca et al., 2004).

Serotonin transporter (SLC6A4) is perhaps the best-studied gene in psychiatric genetics, with associations reported for a broad range of diagnoses and traits (Anguelova et al., 2003a, b). When the studies of the 'long' allele of HTTLPR are combined, the pooled odds ratio for the long allele in ADHD samples is 1.31 (95% CI 1.09–1.59). Two family-based association studies examined a silent SNP (G861C) in the gene coding for the serotonin HTR1B receptor. In predominantly Caucasian samples, both studies found over-transmission of the "G" allele, though this finding only reached statistical significance in the very large study which reported pooled results from four sites (Hawi et al., 2002). The association between the over-transmission of the "G" allele and ADHD reached significance as well in a study that analyzed paternal transmission (Quist et al., 2003). The pooled odds ratio for the G861C SNP is 1.44 (95% CI 1.14–1.83).

While these findings on candidate genes are interesting, it is important to note that these genes are of low effect size and explain only approximately 2% of the variance in symptomatology. Further, most of these studies are based on just one of possibly many functional polymorphic variations in specific genes of interest and, unfortunately, most results are inconsistent.

Environmental influences

Before turning to a discussion of the complicating factors in genetic studies, relevant environmental influences will be summarized. Several environmental risks for ADHD have been identified and these are all good candidates for moderation of genetic influences. These environmental risks can be grouped into three categories: 1) pre- and perinatal influences, such as prematurity, low birth weight, pregnancy and birth complications (Hille et al., 2001; Botting et al., 1997; Mick et al., 2002a, b), and mother's use of alcohol or tobacco during pregnancy (Milberger et al., 1996); 2) parental and family factors such as critical expressed emotion versus expressed warmth, inconsistent parenting, parental divorce, family conflict and early institutional rearing (Rutter et al., 2001; Woodward et al., 1998); and 3) acquired neurobiological risks such as closed head trauma and exposure to lead (Thomson et al., 1989; Max et al., 2004; Schachar et al., 2004).

Concerning obstetric adversity, a birth weight lower than 2500 g raises the risk to ADHD about 3–10 times (Breslau et al., 1996; Whitaker et al., 1997). A recent twin study could replicate the association between lower birth weight and increased levels of behavior problems in children as an independent main effect. Interestingly, and in addition, there was an interaction between birth weight and genetic factors in that lower birth weight was associated with decreased genetic influence (Van Os et al., 2001). Obstetric adversity may be co-dependent of the characteristics of the fetus and may mediate genetic risks, as has been shown in the case of autism (Glasson et al., 2004; Bolton et al., 1997). For example, non-affected siblings were more similar to their affected probands than to controls in their profile of birth complications (Glasson et al., 2004). Studies among clinically referred children report particularly high rates of toxemia or eclampsia, maternal illness, maternal psychological stress, bleeding, lengthy labor or delivery, and undue weight loss or gain of the pregnant mother for children with ADHD compared to control children (Milberger et al., 1997; Sprich-Buckminster et al., 1993).

Concerning family functioning, children with ADHD live in a family-environment characterized by marital discord, high rates of parental psychiatric disorder, and low occupation status much more often than controls (Scahill et al., 1999). Family adversity factors as marital discord, low SES, large family size, paternal criminality, maternal mental disorder, and foster placement increased the risk for ADHD and predicted for comorbid disorders, cognitive impairment, and psychosocial dysfunction (Biederman et al., 1995). It is important to appreciate that these associations between family-environment and ADHD are difficult to interpret since a number of these factors such as parental disorder may both reflect genetic transmission and exert an adverse influence through the alteration of parent-child relationships. Further, the family

adversities may well be, in part, the consequence of having a problematic child with ADHD rather than the cause of it. Finally, these associations between factors that are defined at the level of the family as a whole, are hard to reconcile with the importance of the nonshared rather than the shared environment, as is shown by twin studies. For example, in an Australian twin study, non-shared environmental influences accounted for about 15% of the variance of ADHD symptoms (Rhee et al., 1999).

Therefore, we will review now work on disrupted parent-child relationships and hyperactivity/aggression. Careful characterization of parent-child relationships of hyperactive children derived from community studies points to the importance of abnormalities of affective tone (especially hostile expressed emotion, HEE) and impairment of parental coping skills (Taylor et al., 1991; Woodward et al., 1998). HHE was seen in 33% of mothers of hyperactive children and in 6% of healthy controls. Poor coping skills were seen in 44% of mothers of hyperactive children and 15% of healthy controls (Woodward et al., 1998). These two sets of figures give odds ratios for the two environmental factors of 7.7 and 3.8 respectively. Hostile parent-child interactions were further found to predict the longitudinal course of children with hyperactivity (Rutter et al., 1997).

Further research is needed to determine whether these are proximal risks effecting the brain directly (e.g. toxicity from alcohol), act indirectly (e.g. maternal drinking correlates with poor parenting and poor parenting is proximal risk), are genetically correlated with the genotype of the mothers (e.g. mothers with ADHD are more prone to smoke during pregnancy than mothers without ADHD) or are genetically correlated with the ADHD proband genotype (e.g. ADHD behavior evokes hostile expressed emotion in the parent).

Complicating factors

Discovering genes involved in ADHD is complicated by several factors (Table 2). The further unraveling of the genetic architecture of ADHD will depend to a large extent on how well these complicating factors are handled and even used. The first one is that the identification of genes of small main effects requires the use of very large sample sizes (Risch et al., 1996). These can only be collected by large consortia, and several of these have been formed over the past years, among which the International Multi-center ADHD GENetics Project (IMAGE)

Table 2. Complicating factors in genetic studies in complex genetic disorders like ADHD

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1. Multiple genes of small main effects
 2. The relevant phenotype is unknown
 3. Clinical heterogeneity
 4. Genetic heterogeneity
 5. Gene-environment correlation
 6. Gene-environment interaction
 7. Importance of endophenotypes
 8. Importance of developmental factors
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Consortium (Asherson, 2004). This consortium under the leadership under Steve Faraone includes more than 10 sites in Europe and aims to collect at least 2000 ADHD families. From these, the 400 most informative concordant pairs and the 400 most informative discordant pairs will be used for initial genomewide linkage studies. Collaborative work has been further facilitated by the ADHD Molecular Genetics Network (NIH grant to Steve Faraone) which comprises investigators from around the world who currently study the genetics of ADHD and meet on a regular basis. A second forum is the EUropean NETwork of HYperactivity DISorders (Eunethydis) (leadership Joe Sergeant) which also has yearly meetings to discuss potential and actual collaboration.

A second factor is that it is unknown on which phenotype molecular-genetic studies should focus. Traditional psychiatric categories as defined in classification schemes as DSM-IV and ICD-10 have been developed for clinical purposes but have not been selected for being relevant phenotypes for genetic research. Twin studies for example indicate that ADHD, and oppositional-defiant/conduct disorder share a substantial amount of genetic factors in childhood (Silberg et al., 1996). There are several approaches to improve the definition of the relevant phenotype for genetic studies. One is based on the work of Risch (1990a, b), who proved that the statistical power of a linkage study increases with the magnitude of risk ratios computed by dividing the affection rate among each relative type (e.g., siblings, offspring) to the rate of affection in the population. These ratios have been called “lambdas.” It was shown that the power depends only on lambda and that defining disease status in a manner that increased lambda would increase the power of linkage studies. According to this logic, Faraone et al. (2000) demonstrated that lambdas were greater if the ADHD proband also has conduct disorder (4.5 and 8.6) and were even greater if the proband has persistent ADHD (17.2 and 19.5). The highest lambdas were found when the proband had both persistent ADHD and CD (25.0–25.9). Another strategy is to fully exploit the potential of twin studies to separate genetic from environmental influences. Though aggregate constructs of ADHD were shown to have heritability as high as 0.80 (see above), similar heritability estimates would not necessarily apply to the single items that are included in these constructs. Twin analyses on single items could afford further information on the decomposition of genetic and environmental influences at the item level, and result in the construction of more “pure” genetically relevant phenotypes. This strategy has been underused so far. A third strategy is the use of newer multivariate techniques as latent class analysis on ADHD symptoms in twin designs. Such a latent class analysis was applied to data obtained from parents on the 18 DSM-IV ADHD symptoms in 4,036 female twins age 13–23 years in a population sample in Missouri (Todd et al., 2001). The latent-class analysis was most compatible with the existence of three mild and three severe classes of ADHD symptoms in the general population. Unlike DSM-IV subtypes of ADHD, latent-class ADHD subtypes appear to be independently transmitted in families. These classes may be more appropriate targets for molecular genetic studies of ADHD. In another twin dataset the inclusion of sluggish cognitive tempo items markedly changed ADHD symptom associations for boys and girls in a factor analytic framework. In contrast, latent class subtyping of ADHD shows limited impact of the inclusion of sluggish cognitive tempo items, emphasizing the very

different assumptions about underlying continua of behavior rather than discrete classes that distinguish the two approaches (Todd et al., 2004). So far, latent class subtypes of ADHD have not been used in genetic linkage studies.

Linked to the previous issue of the definition of the phenotype is that of clinical heterogeneity, i.e. that different siblings in a given family may have a different clinical presentation. For example, one sibling may present with one of the ADHD subtypes, whereas another sibling may have dyslexia without ADHD and a third sibling may have autism spectrum disorder (ASD) with comorbid ADHD. The challenges but also opportunities of clinical heterogeneity have not been met addressed sufficiently, particularly in terms of the overlap between ADHD, ASD and dyslexia. Many children with ASD suffer from inattention, hyperactivity and impulsivity to an extent that clinical management of these ADHD-like symptoms is warranted (Handen et al., 2000; Quintana et al., 1995). Re-analyses of the results of population studies on deficits in attention, motor control and perception (DAMP, i.e. a combination of ADHD and perceptual-motor problems) also revealed a strong overlap between severe DAMP and ASD (Kadesjo et al., 1999; Gillberg, 1992). In a similar way, many children with Attention Deficit Hyperactivity Disorder (ADHD) have associated social deficits that are not part of the core symptoms of inattention, hyperactivity and impulsivity that define the disorder. In a study of social disability in ADHD the majority of a sample of 140 boys with ADHD had some degree of difficulty in the social domain (Greene et al., 1996); 22% even qualified as socially disabled, as compared to none of a group of 120 normal controls. In another study, the Children's Social Behavior Questionnaire (CSBQ) was used to compare social deficits in children with ASD, children with ADHD and normal controls (Luteijn et al., 2000a, b). Children with ADHD were characterized by significant social deficits in social interaction and communication and by an increase in stereotypic and restricted behavior, in comparison with normal controls. Although these deficits were significantly more prominent in children with ASD, it appears that there may be an overlap in social deficits between subjects with ASD and ADHD (Luteijn et al., 2000a, b). This all suggests that by subtyping families with (multiple) ASD cases on ADHD characteristics and by subtyping families with (multiple) ADHD cases on ASD characteristics, one can achieve more homogeneous samples and obtain stronger signals in molecular-genetic studies and refine areas of the genome that are implicated in both disorders (Table 1). Similar considerations apply to the subtyping of dyslexia samples for ADHD and of ADHD samples for dyslexia (Loo et al., 2004).

A fourth factor is that of genetic heterogeneity, i.e. different sets of genes may be responsible for risk in different families. This locus heterogeneity may reduce power to detect linkage in traditional affected sibpair studies. On the other hand, the QTLs associated with ADHD are expected to be common genetic variants that are found across human populations (Wright et al., 1999; Risch, 2000). Thus, if population heterogeneity does exist, it is expected to lead to differing prevalence of QTLs in different groups, rather than presence or absence. In ADHD, the prevalence of the DRD4 7-repeat allele, which has been associated with ADHD, varies among populations (Chang et al., 1996). We expect this will be true of other ADHD susceptibility alleles because they

are likely to be common alleles, which cause minor, additive deviations in neurodevelopment or neurotransmission. In spite of this, genetic heterogeneity points to the importance of genetic designs which are complementary to affected sibpair designs, such as those using extended 3-generation pedigrees.

Fifth, a full understanding of the genetics of complex behavioral disorders like ADHD will require insights into how environmental risk factors combine with genes to influence the disorder and its clinical features. Some genes might affect ADHD by influencing sensitivity to environmental risks (gene-environment interaction, $G \times E$) or modifying the probability of exposure to environmental risks (gene-environment correlation, rGE). Some other environmental risks may increase susceptibility to ADHD independent of genotype. The potential role of $G \times E$ effects contributing to complex behavioral disorders has recently been demonstrated by two reports from the Dunedin Multidisciplinary Health and Development Study on antisocial behavior and depression in which functional polymorphisms in candidate genes moderated the effects known of environmental stressors, with MAOA moderating the influence of parental maltreatment on antisocial behavior (Caspi et al., 2002) and the serotonin transporter gene moderating the influence of stressful life events on depression (Caspi et al., 2003). Neither of the two genes investigated showed main effects with the behavioral phenotypes in the Dunedin dataset, illustrating the important point that gene associations may be missed if environmental measures are not taken into account. To date, few molecular genetic studies of ADHD have incorporated environmental risk measures. Kahn et al. (2003) found that in pre-school children, hyperactivity-impulsivity and oppositional behavior were associated with the DAT1 10-repeat allele, but only when the child was also exposed to maternal prenatal smoking. Another study explored the possibility of an interaction between the DRD4 gene and season of birth (Seeger et al., 2004). A seasonal pattern of birth has been proposed for different subtypes of ADHD. Therefore, in a subgroup of children with ADHD and conduct disorder, and in healthy controls, children carrying the 7-repeat allele of DRD4 showed different relative risks for developing ADHD and comorbid conduct disorder, depending on the season of birth. This suggests the very likely hypothesis that ADHD, as a multifactorial disorder, may result from variations in genes which have small main effects but whose effects are conditional upon exposure to environmental risk and may be strongly amplified by these environmental risks. If risk exposure differs among participants within a sample, genes may account for little variation in the phenotype. Failure to take account of environmental risk factors in previous genetic studies may be responsible for part of the non-replication results. When exposure to environmental risks differs significantly between samples, candidate genes or regions may fail replication.

An additional strategy is to address heterogeneity at the level of endophenotypes. Endophenotypes are latent traits that are heritable, share genetic loading with the disease phenotype, and are probabilistically related to the disease phenotype as defined in DSM-IV or ICD-10 (Gottesman et al., 2003; Skuse, 2001; Leboyer et al., 1998). These latent traits, which can be measured at a physiological, neurobiological, or cognitive level, may be more closely linked to the underlying genetic factors than the behavioral phenotype and that they

Fig. 1. Outline of the principle of the endophenotype. A smaller set of genes may be involved in the endophenotype than in the complex behavioral trait of clinical disorder

mediate gene-clinical phenotype pathways (see Fig. 1). A smaller set of genes may be involved in the endophenotypes than in the complex behavioral trait or clinical disorder. Endophenotypes may improve the power of molecular genetic studies and may also provide a means of parsing genetic heterogeneity. After many years of searching for one single simple neuropsychological deficit there is a growing realization that ADHD is probably best conceptualized as a neuropsychologically heterogeneous condition with differentiable neuropsychological pathways linking specific putative causes to the clinical phenotype (Sonuga-Barke, 2003). These are some studies that suggest that familial ADHD may represent a form of ADHD characterized by a deficient response inhibition. In a study that included ADHD probands with a family history of ADHD, their nonaffected siblings, and normal controls matched for age and IQ, the nonaffected siblings were as impaired in measures of response inhibition as the affected probands when compared to the normal controls (Slaats-Willems et al., 2003). Subjects with ADHD who had a family history of ADHD performed significantly worse on measures of response inhibition than subjects with ADHD without such a family history (Seidman et al., 1995). In addition, children who exhibited poor inhibition (on the stop signal task) were significantly more likely to have a first-degree relative with ADHD than were the children with ADHD who exhibited good behavioral inhibition (Crosbie et al., 2001).

The influence of increased familial risk for ADHD has also been studied on measures of brain morphology (Durstun et al., 2004). Both subjects with ADHD and their unaffected siblings displayed reductions in right prefrontal gray matter and left occipital gray and white matter of up to 9.1%. Right cerebellar volume was reduced by 4.9% in subjects with ADHD but not in their unaffected siblings. A 4.0% reduction in intracranial volume was found in subjects with ADHD, while a trend was observed in their unaffected siblings. Thus, the volumetric reductions in cortical gray and white matter in subjects with ADHD were also present in their unaffected siblings, suggesting that they are related to an increased familial risk for the disorder. In contrast, the cerebellum is unaffected in siblings, suggesting that the reduction in volume observed in subjects with ADHD may be more directly related to the pathophysiology of this disorder

(Durstun et al., 2004). A further study on the same data-set reported that the DAT1 gene, a gene expressed predominantly in the basal ganglia, preferentially influences caudate volume, whereas the DRD4 gene, a gene expressed predominantly in the prefrontal cortex, preferentially influences prefrontal gray matter volume in a sample of subjects including subjects with ADHD, their unaffected siblings, and healthy controls (Durstun et al., 2005). This demonstrates that, by constraining investigations by prior knowledge of gene expression and by using endophenotypes, such as measures of brain morphology, we may begin to map out the pathways by which genes influence behaviour.

Finally, genetic studies in ADHD have disregarded the importance of developmental factors. Different genes may be operating at different ages or developmental stages. In a longitudinal twin study, the relatively high stability of ADHD symptoms over a 5-year period between age 8/9 and age 13/14 year was found. This continuity was mainly due to the same genetic effects operating at both points in time. Change in symptoms between childhood and early adolescence was to a large extent due to new genetic effects in early adolescence but also due to new nonshared environmental effects that became important during adolescence (Larsson et al., 2004). Rather similar results were obtained in another longitudinal twin study which spanned ages 3, 7, 10, and 12 year and used maternal ratings of problem behaviors (Bartels et al., 2004). Stability in externalizing behaviors was accounted for by genetic and shared environmental influences. The genetic contribution to stability for externalizing behaviors was 60% and resulted from the fact that a subset of genes expressed at an earlier age was still active at the next time point. In addition, significant age-specific influences were found for all components, indicating that genetic and environmental factors also contributed to changes in problem behavior. Genetic studies in ADHD should be enriched with a developmental perspective, and explore whether variables as age of onset and severity of disease at various points in time (rather than persistence *per se*) are relevant developmental endophenotypes.

Concluding remarks

Genetic research of complex disorders like ADHD is one of the most powerful tools to increase our insight into the underlying pathophysiology of the disorder. In the absence of direct neural tissue such as obtained post-mortem or by biopsy, no direct clues as to the neurochemical or cellular or molecular changes at the level of the brain are available. The identification of relevant genes opens new avenues to approach the cellular and molecular base of the disorder. Ultimately, this has the potential to individualize treatment, to facilitate prevention, and to develop new and effective treatments.

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