Genetic basis of attention deficit and hyperactivity

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Background Hyperkinetic disorder or attention-deficit hyperactivity disorder (ADHD) is an important clinical condition.

Aims The research evidence for a genetic contribution to ADHD is reviewed.

Method Measurement of the phenotype, the extent to which attention deficit and hyperactivity are heritable and molecular genetic findings are discussed. Future research directions are also considered.

Results ADHD is a familial disorder. Available adoption evidence suggests genetic influences are important. Twin studies have primarily focused on trait measures which have consistently been found to be highly heritable. Molecular genetic studies of clinical disorder so far have suggested the involvement of the dopamine DRD-4 receptor gene and dopamine transporter gene (DAT1). However, these findings await further replication.

Conclusions Advances in psychiatric genetics and current research interest in the genetics of ADHD should improve our understanding of aetiological factors and have an impact on treatment.

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Hyperkinetic disorder or attention-deficit hyperactivity disorder (ADHD) is a highly disabling condition which has an onset in early childhood. It is characterised by marked and pervasive inattention, overactivity and impulsiveness and affects approximately one in 200 children in the UK (Taylor, 1994). Children with ADHD not only experience educational failure, problems with relationships and poor self-esteem, but are also at increased risk of psychiatric and social difficulties in adulthood. Moreover, there is increasing recognition that ADHD symptoms may persist into adult life. Recently there has been growing interest in the genetic basis of ADHD and an increasing body of research in this area. The aim of this article is to review the evidence for a genetic contribution to hyperactivity. We will first discuss the phenotype definition, consider the extent to which hyperactivity is heritable and then examine recent molecular genetic findings. Finally, we will discuss future directions for research.

DEFINING HYPERACTIVITY: DIAGNOSTIC CRITERIA, MEASURES AND RATERS

The success of genetic studies will depend on how well the phenotype is defined. This represents a significant problem in psychiatry, where phenotypes are defined on the basis of reported symptoms, rather than objective measures, such as physical signs or biochemical abnormalities. Despite major improvements in the reliability of psychiatric diagnoses (including ADHD), clinically acceptable definitions of disorders may not represent genetically valid phenotypes. Moreover, a number of uncertainties remain about the best way to conceptualise hyperactivity. These issues need to be considered carefully in the design and interpretation of genetic studies of ADHD.

Diagnostic differences

Transatlantic differences in diagnosing hyperactivity continue to pose difficulties when comparing results from different studies. The ICD–10 criteria for "hyperkinetic disorders" include persistent symptoms of inattention (six symptoms), hyperactivity (three symptoms) and impulsivity (one symptom) present in more than one setting (World Health Organization, 1992). In contrast, the DSM–III definition of "attention deficit disorder" (ADD) and the DSM–III–R definition of "attention-deficit hyperactivity disorder" (ADHD) are much broader, in not requiring pervasiveness of symptoms, or the presence of symptoms across three symptom areas (American Psychiatric Association, 1980, 1987). Although DSM–IV (American Psychiatric Association, 1994) requires symptoms in two rather than three symptom areas, namely inattention (six symptoms) and overactivity/impulsivity (six symptoms) for a diagnosis of ADHD-combined type, symptoms are needed in only one symptom area for defining inattentive and hyperactive/impulsive subtypes. Thus, ICD–10 criteria define a more severe and less common condition.

Category or dimension

Another unresolved issue is whether hyperactivity is best conceptualised as a behavioural dimension or as a diagnostic category. The diagnostic category of ADHD/hyperkinetic disorder is clinically useful particularly for planning treatment and in predicting prognosis. Moreover, it is a category which has repeatedly been shown to be valid, in terms of clinical correlates (Taylor, 1994). However, as will be discussed, quantitative measures have been widely used in genetic studies and may display greater predictive validity.

Which rater and which setting?

Another uncertainty is whether hyperactivity should be defined in regard to the setting in which symptoms occur (home, school, elsewhere or pervasive) and of who the informant should be, that is parent or teacher.

Overall these issues are important to consider when carrying out and interpreting genetic studies. However, results emerging from genetic studies are increasingly informing us about the phenotypic definition of hyperactivity, thereby providing an

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empirical basis for resolving some of these measurement issues.

FAMILY STUDIES: CONSISTENT EVIDENCE THAT ADHD AGGREGATES IN FAMILIES

Family studies suggest that ADHD is a highly familial condition (see McGuffin *et al*, 1994). Early research showed higher prevalence rates of hyperactivity among biological parents and second-degree relatives of children with hyperactivity, compared with controls. Furthermore, family studies have found that full siblings of affected children show higher rates of hyperactivity than half siblings. Recent research, which addresses several of the methodological limitations associated with the earlier studies, consistently confirm these findings.

In a recent series of family studies, where standardised interviews and operationalised diagnostic criteria were used, relatives of affected male and female probands were found to be at increased risk for the disorder. First-degree biological relatives of male probands were five times more likely to be diagnosed with ADHD than relatives of normal controls. However, the familial transmission of ADHD is also complex given that many family studies have shown that relatives of children with ADHD display an increased risk for a number of other psychiatric disorders, such as conduct disorder, depression, anxiety and learning disorders (see McGuffin *et al*, 1994).

COMORBIDITY: EVIDENCE FROM FAMILY STUDIES

Several family studies have investigated the effect of co-existing disorders on the familiality of hyperactivity. These studies suggest that relatives of probands with ADHD and comorbid conduct disorder are at greatest risk for ADHD. Furthermore, the high prevalence rate of antisocial disorders appears to occur among first-degree relatives of probands diagnosed with ADHD and comorbid conduct disorder, rather than among relatives of children diagnosed with 'pure' ADHD. These findings suggest that ADHD and comorbid conduct disorder may represent a separate familial subtype. Furthermore, research indicates that ADHD and depression may share common familial vulnerabilities whereas ADHD diagnosed with anxiety or learning disorders may be aetiologically independent.

In summary, family studies provide substantial evidence that ADHD is a highly familial condition that commonly coexists with other psychiatric disorders. However, the familial transmission of ADHD may be explained by shared environmental factors such as social disadvantage, as well as by genes. Therefore, to examine the genetic contribution to ADHD, additional evidence should be gathered from twin and adoption studies, which distinguish between genetic and environmental effects.

TWIN STUDIES: EVIDENCE THAT HYPERACTIVITY AND INATTENTION ARE HERITABLE

The methodological design of twin studies enables us to examine the extent to which traits and disorders are heritable, as well as to estimate the contribution of shared and non-shared environmental influences. The basic premise underlying twin research is that monozygotic (MZ) twins are genetically identical, whereas dizygotic (DZ) twins share on average 50% of their segregating genes. Thus, for a genetically influenced trait or disorder, MZ twins will be more similar than DZ twins, assuming that MZ and DZ twins share environment to the same extent. In simple terms, we would expect the MZ correlation (r) or concordance rate for a given trait or disorder to be greater than the DZ correlation.

There have been a number of twin studies which have primarily focused on hyperactivity defined as a trait. Most of this work has been based on questionnaire measures of hyperactivity symptoms and in particular the three hyperactivity items from the Rutter A questionnaire (Rutter *et al*, 1970) ("squirmy", "restless", "cannot settle").

Recent studies which address previous methodological limitations, by incorporating larger, representative samples and psychometrically sound measures, consistently report higher correlations in hyperactivity/inattention scores for MZ twins, than for DZ twins. Table 1 shows that heritability estimates range from 0.39 to 0.91 for reported symptoms of ADHD, which indicate that genetic factors account for a substantial amount of variance.

GENES INFLUENCE NORMAL VARIATION IN HYPERACTIVITY SCORES AND EXTREME SCORES

The studies listed in Table 1 have largely been based on population-based samples of twins and therefore inform us that normal variation in hyperactivity symptoms is genetically influenced. For clinicians, a critical issue is whether genetic factors also influence extreme scores. The genetic and environmental influences on extreme scores or diagnostic categories may not necessarily be the same as those on normal variation (e.g. if genes influenced normal variation whereas environmental adversity was more important for clinical disorder). One method of examining this issue is by analysing twin data using a regression method. Four studies have used this approach and shown that extreme scores are also highly heritable, with heritability estimates ranging from 0.73 to 0.91 (Gillis *et al*, 1992; Stevenson, 1992; Gjone *et al*, 1996; Levy *et al*, 1997). Moreover, there is some evidence to suggest that a broad categorical definition of hyperactivity (not clinical disorder) defined using questionnaire measures (Goodman & Stevenson, 1989; Levy *et al*, 1997) is also heritable. Thus, there appears to be no distinction between hyperactivity symptoms across the normal range and extreme scores, at least in terms of genetic aetiology.

IMPORTANCE OF RATER AND SITUATION EFFECTS

A consistent and perplexing finding from twin studies has been the observation of a low DZ twin correlation. This has been particularly evident in studies which have used the maternally-rated Rutter A questionnaire (Goodman & Stevenson, 1989; Thapar *et al*, 1995; Silberg *et al*, 1996; Eaves *et al*, 1997), where DZ twin correlations have been found to be negative (and MZ and DZ twin variances differed). Clearly there is no plausible biological explanation for a negative DZ twin correlation. However, genetic analyses indicated that these findings could partly be explained by sibling competition effects, where the behaviour or symptoms of one twin has an inhibitory influence on the symptoms of the other twin (Thapar *et al*, 1995; Eaves *et al*, 1997) or by rater contrast effects. More recent analyses utilising

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Table 1 Summary of twin studies of hyperactivity and inattention

Authors	Twin sample characteristics	Phenotypic measures	Correlations (continuous measures)		Concordance rates (categorical measures)		Heritability estimates h^2
			rMZ	rDZ	MZ (%)	DZ (%)	
Goodman & Stevenson (1989); Stevenson (1992)	102 MZ 111 same-sex DZ twins, aged 13 years	Rutter A (Mother) Rutter A (Father) Rutter B (Teacher)	0.68 0.48 0.62	−0.08 0.21 0.26			>1.0 0.54 0.72
					51.0	33.0	0.64 (category) 0.75 (extreme scores)
Gillis *et al* (1992)	37 MZ 37 DZ twins, with reading disability aged 8–20 years	DICA Interview (Parent) based on DSM–III–R			79.0	32.0	0.91 (extreme scores)
Edelbrock *et al* (1995)	99 MZ 82 same-sex DZ twins aged 7–15 years	CBCL (Mother) *Attention problems scale*	0.68	0.29			0.66
Thapar *et al* (1995)	113 MZ 85 same-sex DZ 83 opposite-sex DZ twins aged 8–16 years	Rutter A (Mother)	0.61	−0.10			0.88
Gjone *et al* (1996)	327 MZ 389 same-sex DZ twins aged 5–15 years	CBCL (Mother) *Attention problems scale*	0.72–0.78	0.21–0.45			0.73–0.79 0.87 (extreme scores)
Levy *et al* (1997)	597 MZ 602 same-sex DZ 435 opposite-sex DZ twins aged 4–12 years	DSM–III–R ADHD Rating Scale (Mother)	0.88	0.49	82.4	37.9	0.75 (trait) 0.91 (extreme scores)
Eaves *et al* (1997)	689 MZ 371 same-sex DZ 295 opposite-sex DZ twins	Rutter A (Mother)[1]	0.49–0.51	−0.05–0.16			0.60–0.80
Sherman *et al* (1997)	194 MZ boys 94 DZ boys aged 11–12 years	DICA–R (Mother) *inattention* *impulsivity/ hyperactivity* MTFS TRF[2] inattention impulsivity/ hyperactivity	0.70 0.92 0.78 0.69	0.30 0.32 0.57 0.42			0.69 0.91 0.39 0.69

DICA, Diagnostic Interview for Children and Adolescents.
1. Paper also reports correlations for teacher and father Rutter scales and Child and Adolescent Psychiatric Assessment interview.
2. Minnesota Twin Family Study Teacher Rating Form (MTFS TRF) includes items from the Conners scale, Rutter's B scale and DSM–III and DSM–III–R criteria.

parent and teacher ratings suggest the most likely explanation for low DZ correlations is maternal contrast effects. The potential for maternal bias is an important issue in the design of twin research and emphasises the need for multiple informants in genetic studies.

This issue will be of greater importance in defining the hyperactivity phenotype for molecular genetic studies. The detection of susceptibility genes requires familial resemblance for a trait and is thus problematic for a phenotype that has a DZ correlation close to zero.

GENETIC EXPLANATIONS OF COMORBIDITY

Twin studies also allow us to examine to what extent the covariation or correlation of two or more traits (e.g. hyperactivity symptoms and conduct symptoms) can be explained by a shared genetic or environmental aetiology. To date, we have evidence to suggest that the genes that influence conduct disorder symptoms are the same as those that contribute to hyperactivity (Silberg *et al*, 1996). Similarly, reading disability and hyperactivity symptoms also appear to share a common genetic aetiology (Gillis *et al*, 1992; Stevenson *et al*, 1993). However, it remains uncertain

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whether these findings would also be applicable to clinical disorders.

ADOPTION STUDIES: ADDITIONAL EVIDENCE FOR GENETIC TRANSMISSION OF HYPERACTIVITY

The fundamental assumption underlying adoption studies, is that a genetically influenced disorder will show a greater prevalence among biological relatives of affected children, than among adoptive relatives.

Early adoption studies (see McGuffin *et al*, 1994) found significantly higher rates of hyperactivity among biological parents of children with hyperactivity (7.5%) compared with adoptive parents (2.1%). Similarly, greater concordance rates have been reported for adopted-away full siblings of children with hyperactivity, than for half siblings. Adoption research has also found that biological parents of hyperactive children demonstrate significantly poorer performance on cognitive measures of attention, compared with adoptive parents. Although few adoption studies have been conducted and those published show methodological flaws, the findings when taken together strongly suggest a genetic basis for both hyperactivity and inattention.

MOLECULAR GENETICS OF ADHD: CURRENT APPROACHES

Overall, genetic factors have been shown to be important across a variety of studies. There is thus a compelling argument for now searching for susceptibility genes at a molecular level. As for other psychiatric disorders, there are a variety of strategies which could be used to search for susceptibility loci for hyperactivity and these have been described in detail elsewhere (McGuffin *et al*, 1994). Affected sib-pair linkage approaches where large samples of multiply-affected siblings are collected, are being widely used to search for susceptibility loci for complex disorders such as schizophrenia, bipolar affective disorder and autism. This method is based on examining whether the number of alleles shared by siblings at a particular marker locus is greater than expected (linkage) and testing for linkage with markers spread across the whole genome. Although this methodology has proved to be fruitful for some conditions, for example diabetes, very large samples are needed to detect genes of more minor effect. Given that the estimated relative risk for first-degree relatives for ADHD is only modest, a very large number of affected sibling pairs would be needed to detect linkage.

In association studies the frequencies of marker alleles (alternate forms of a gene at the same locus) among unrelated affected individuals are compared with those of a control group. However, positive findings of association may reflect other differences between the cases and controls (population stratification) but this problem can be overcome by using family-based association studies, where parental genotype information is used as the control. Association studies are particularly suitable for detecting susceptibility genes of more minor effect, but where the marker is either very close to the susceptibility locus or is actually the susceptibility gene itself. Thus, at present, an association approach is favoured where there is evidence to suggest good candidate loci. There is an empirical rationale for proposing a number of candidate loci for hyperkinetic disorder with the main focus for investigation concentrated upon genes of the catecholamine biosynthetic pathway. This is largely due to the therapeutic effect of psychostimulant drugs such as methylphenidate hydrochloride. There is consistent evidence that around 70% of affected children show a rapid symptomatic improvement with methylphenidate which increases extracellular dopamine levels.

The current interest in candidate genes involved in dopaminergic pathways in combination with the greater ease of collecting unrelated cases rather than multiply-affected family members for hyperkinetic disorder may explain to some extent why most of the published findings to date are based on association studies.

MOLECULAR GENETIC FINDINGS FOR ADHD: INITIAL PROMISING RESULTS WHICH NEED REPLICATION

To date, genes encoding the dopamine transporter (DAT1) and the dopamine DRD-4 receptor have both been implicated.

Dopamine transporter gene DAT1

DAT1 is a particularly attractive candidate gene given that methylphenidate is known to inhibit the dopamine transporter mechanism and DAT1 knockout mice exhibit features of motor overactivity. One of the first associations to be reported was in a US sample (Cook *et al*, 1995) where a significant increase in the frequency of the 480 base pair allele of the dopamine transporter gene DAT1 was found in a case–control study of 49 patients with ADHD, as defined by DSM–III–R criteria. This association has now been replicated in an Irish family-based association study of 40 children with ADHD (Gill *et al*, 1997).

Dopamine receptor DRD-4 gene

The other group of published studies has focused on the dopamine D4 receptor gene. Swanson *et al* (1998) reported a positive association of the DRD-4 7 repeat allele in a Californian family-based study of 52 cases with DSM–IV ADHD (combined type). This extended and replicated earlier case–control study findings. However, the authors were unable to replicate findings of an association with DAT1. There have since been two further published reports of a positive association of DRD-4 with ADHD. In one of the studies, which was based on 133 families of children with DSM–III–R/DSM–IV diagnosed ADHD (Smalley *et al*, 1998), the DRD-4 7 repeat allele conferred a 1.5-fold increased risk for ADHD. The other study (Rowe *et al*, 1998), when using a case–control design, showed a significant association of the DRD-4 7 repeat allele with questionnaire-defined categorical (combined and inattentive types) and dimensional measures of ADHD. However, other analyses in these two studies revealed mixed results and a third case–control study of 41 children with ADHD failed to replicate these findings (Castellanos *et al*, 1998).

The DRD-4 and DAT1 findings are important and exciting, particularly as the results have been replicated by more than one group. However, at this early stage, caution is required. In the positive studies, DRD-4 and DAT1 account for only part of the genetic contribution towards ADHD. Moreover, Table 2 shows that findings for DRD-4 7, DAT1-480 and ADHD are mixed. Nevertheless, positive results should also not be prematurely dismissed on the basis of apparent non-replication. So far reported results have been based on small sample sizes which do not have sufficient statistical power to detect the effect sizes for DRD-4 and DAT1 reported in the first positive studies. Overall, the findings emerging from molecular genetic studies

Table 2 Molecular genetic studies of attention-deficit hyperactivity disorder

Authors	Sample (*n*), place	Association/linkage finding	Diagnostic classification	Locus	Allele	χ^2	*P*
Cook *et al*, 1995	49, Chicago	Positive	DSM–III–R	DATI	480 bp	7.29	0.007
Palmer *et al*, 1997[1]	77, California	Positive (for males)	DSM–IV	DATI	480 bp	not reported	0.07
Gill *et al*, 1997	40, Ireland	Positive	DSM–III–R	DATI	480 bp	6.07	0.014
Waldman *et al*, 1997[1]	90, USA	Positive (hyperactive–impulsive symptoms)	DSM–IV (symptom scores)	DATI	480 bp	not reported	not reported
La Hoste *et al*, 1996	39, California	Positive	DSM–IV	DRD-4	7 r	7.7	<0.01
Asherson *et al*, 1997[1]	UK	Negative	ICD–10	DATI	480 bp	not reported	not reported
				DRD-4	7 r	not reported	not reported
Smalley *et al*, 1998	133, California	Positive TDT (other mixed findings)	DSM–III–R/ DSM–IV	DRD-4	7 r	4.85	0.03
Castellanos *et al*, 1998	41, Maryland	Negative	DSM–III–R	DRD-4	7 r	0.06	0.81
Sunohara *et al*, 1997[1]	40 adults, Canada	Positive	DSM–IV	DRD-4	7 r	not reported	0.049
Swanson *et al*, 1998	52, California	Positive	DSM–IV	DRD-4	7 r	4.65	0.035
Rowe *et al*, 1998	70, Arizona/Georgia	Positive case–control (mixed TDT findings)	DSM–IV (questionnaire based)	DRD-4	7 r	5.9	<0.01

1. Abstracts/presentations from World Congress of Psychiatric Genetics (October 1997). *American Journal of Medical Genetics*, **74** (6).
TDT, transmission disequilibrium test.

of ADHD look promising but more work based on larger studies is needed before this information can be utilised in clinical practice.

GENES FOR HYPERACTIVITY TRAIT MEASURES – A MOVE TOWARDS QUANTITATIVE TRAIT LOCI STUDIES

All published molecular genetic studies of ADHD to date have been based on clinical samples, in which hyperactivity/ADHD has been diagnosed as a disorder. As for other complex disorders, aetiological and clinical heterogeneity are also likely to be important factors which may to some extent account for non-replication of findings. We have already highlighted differences in diagnostic definitions but it is difficult to ascertain to what extent additional influences such as referral bias, the ages, genders and IQs of children in the clinical samples, degree of comorbidity and the role of environmental factors (such as the socio-economic status of the catchment area) may result in different study populations. This too may account for non-replication of results.

An alternative approach is to search for susceptibility genes for hyperactivity defined as a continuous measure or trait, rather than as a clinical disorder. This is particularly appealing given that twin studies have consistently shown that dimensional measures of hyperactivity are so highly heritable. Moreover, searching for genes for a trait in a normal population overcomes difficulties of possible confounding factors associated with referral.

There has been recent interest in the molecular genetic basis of quantitative measures of behaviours and personality traits similar to those seen in ADHD, in particular, novelty-seeking, which is characterised by traits such as impulsivity and excitability. Separate groups have shown a significant association with the DRD-4 7 repeat allele and higher novelty-seeking test scores. However, other researchers have not replicated these findings, although this may to some extent reflect sample differences (e.g. clinical samples versus normal populations) and the use of different measures. Findings from quantitative trait loci studies of childhood hyperactivity have yet to be published and will represent an important development.

CONCLUSION AND FUTURE DIRECTIONS

The contribution of genetic factors

Overall, ADHD, when conceptualised as a clinical disorder appears to be highly familial and available adoption evidence suggests that genetic influences contribute. Twin studies have focused on dimensional measures and there is now convincing evidence that hyperactivity, defined as a trait, is highly heritable. However, none of these studies has examined clinically significant disorder, although there is some suggestion that a broadly defined ADHD category is also heritable.

We have highlighted some of the difficulties in measuring the phenotype. Important issues to be considered in future studies include the choice of measures and rater effects. Given the concerns regarding maternally rated questionnaire measures, it will be essential to include other informants and different types of measures. There has been much interest in attempting to obtain more objective measures of related traits such as attention span and activity levels using, for example, computerised tasks and actigraph measures (Taylor, 1994). However, apart from initial work using traditional psychometric tests (Goodman & Stevenson, 1989), there has been limited twin work examining the genetic contribution to these types of measures. Another issue is whether hyperactivity should be defined as a unitary dimension. Although factor analysis suggests that ADHD symptoms can be subdivided into two distinct dimensions (reflected in DSM–IV), the genetic evidence so far suggests that hyperactivity, impulsivity and inattention are influenced by the same set of genes (Sherman *et al*, 1997). Thus, at present, there is little support, at least from genetic studies, to separate these dimensions.

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Searching for susceptibility genes

Molecular genetic studies of clinical ADHD are now in progress, with initial positive findings for DRD-4 and DAT1. However, these findings still need further replication. Twin evidence strongly favours searching for quantitative trait loci for dimensional measures of hyperactivity and related behavioural traits, and results from these studies are awaited. Given that hyperactivity as a trait is highly heritable and there appears to be no genetic distinction between extreme scores and normal variation, it is reasonable to question whether there is a need, or if it is even valid, for genetic studies to focus on ADHD as a diagnostic category using clinical samples. However, clinicians and patients will need to be informed as to whether susceptibility genes identified for a trait in a normal population, also contribute to clinical disorder and, more importantly, are of relevance for ADHD which is referred to psychiatry services. These add to the argument that we probably need to adopt both approaches, that is examine the genetic basis of the trait and disorder.

If serious attempts at searching for susceptibility genes for clinical disorder are to be made, experience from more established genetics research, for example in schizophrenia and bipolar affective disorder, clearly indicate that national and international pooling of samples will be required. Extremely large sample sizes will be required to detect genes of small effect and generate clinically homogeneous samples, if we are to take into account potential influences such as comorbidity, ADHD subtypes, gender, age, IQ and observable environmental adversity.

Although this review has focused on the role of genetic influences, ADHD is a complex multifactorial disorder and environmental factors will also need to be considered. Unfortunately, relatively little is known about the interplay between genes and environment. The need to incorporate measures of environmental factors within genetically sensitive designs has been emphasised. This will be important even when susceptibility genes are identified, as environmental factors may well play an important protective or mediating role (Taylor, 1994).

There have been rapid advances in psychiatric genetics research and much recent interest in the genetics of ADHD. Knowledge of the genetic basis of ADHD should improve our understanding of the condition and have an impact on clinical work. Families will require up-to-date information and may request genetic counselling. Moreover, positive genetic findings when consistently replicated, will contribute to a greater understanding of the pathophysiology of ADHD and pave the way for more rational types of treatment.

CLINICAL IMPLICATIONS

- Hyperactivity is highly heritable.
- Initial results from molecular genetic studies look promising.
- Further work is needed before results can be incorporated into clinical practice.

LIMITATIONS

- Defining the phenotype remains a problematic issue.
- Most of the evidence that hyperactivity is heritable is based on trait measures.
- Molecular genetic studies have lacked statistical power.

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