Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsiveness. ADHD varies in its clinical presentation and course. The course of ADHD may be influenced by genetic and environmental factors, and there is evidence that genetic factors contribute to the aetiology of ADHD. Genetic and environmental factors do not act in isolation; they interact to influence the development and clinical course of ADHD. Genetic factors contribute to the variability in clinical presentation and course, and there is evidence that susceptibility gene variants, such as those for the dopamine D4 receptor gene, may be associated with ADHD. However, the role of genetic factors is complex, and there are additional risk factors (both genetic and environmental) that may influence the development and clinical course of ADHD. Further research is needed to identify susceptibility genes and to understand their role in the development and clinical course of ADHD.
receptor DRD5 gene has also yielded significant evidence of association, with an estimated odds ratio of 1.24 (Lowe et al., 2004). Finally, the most recent pooled analysis found small but significant association between a dopamine transporter gene variant – a variable number of tandem repeats (VNTR) 10-repeat allele – and ADHD, in which the odds ratio was 1.1 (Faraoe et al., 2005). More recently there have been several reports of association between variants in the SNAP-25 gene and ADHD (pooled OR = 1.19), although the associated variants have differed between studies. This gene became of interest following reports that a SNAP-25-deficient mouse mutant shows hyperactivity. Other gene variants have been examined but these need further study (Thapar et al., 2005b). Thus, replicated genetic findings are emerging, but it is necessary to know more about how variants result in disorder, at a biological and phenotypic level.

**DO THE SAME OR DIFFERENT SUSCEPTIBILITY GENES INFLUENCE THE DEVELOPMENTAL COURSE OF ADHD?**

So far few studies have examined this question. One study has shown that the DRD4 7-repeat risk allele influenced persistence of ADHD over time (El-Faddagh et al., 2004). There has been interest in investigating what gene variants influence antisocial behaviour in ADHD, and here there have been several sets of interesting findings. First, the DRD4 7-repeat allele was found to be associated with antisocial behaviour in ADHD in a joint analysis of data from Cardiff, London and Dublin. These findings suggest that this allele might be important in influencing the course as well as the origins of ADHD. More recently the Cardiff group found that a functional variant in the gene encoding the enzyme COMT (previously found to be associated with measures of prefrontal cognitive functioning) was associated with antisocial behaviour in ADHD but not with ADHD itself (Thapar et al., 2005a). Finally, a variant in MAOA, a gene encoding another enzyme involved in neurotransmitter breakdown, was found to be associated with antisocial behaviour in ADHD but not with ADHD itself (Thapar et al., 2006).

**GENE–ENVIRONMENT INTERACTION**

Attention-deficit hyperactivity disorder and its subsequent developmental course are not entirely explained by genes. There are a number of environmental factors that also appear to be associated with ADHD, two of which have withstood meta-analysis or pooled analyses: exposure to maternal smoking in pregnancy (estimated odds ratio 2.39; Langley et al., 2005) and low birth weight/prematurity (odds ratio 2.64; Bhutta et al., 2002). It is well recognised that not all of those who are exposed to environmental adversity go on to develop ADHD. Gene–environment interaction (G × E), whereby genes operate by influencing sensitivity or response to environmental adversity, is becomingly increasingly recognised as important. To date there have been few published studies examining the contribution of G × E to ADHD and its course. For example, a recent study found that the association between a DAT1 haplotype (combination of risk alleles) and ADHD was stronger when the mother had drunk alcohol during pregnancy (Brookes et al., 2006). Another group suggested that the DAT1 risk allele previously found to be associated with ADHD was only associated with hyperactive-impulsive symptoms in those who had been exposed to maternal smoking during pregnancy (Kahn et al., 2003). In a study that focused on childhood-onset conduct disorder symptoms in ADHD, those who carried the COMT gene risk variant appeared to be more susceptible to the adverse effects of lower birth weight (Thapar et al., 2005a). All these findings now require replication but the evidence so far suggests that some genes may influence the origins and developmental course of ADHD by affecting individual sensitivity to environmental adversity.

In conclusion, genetic factors contribute to ADHD and replicated molecular genetic findings are now emerging. It is, however, important to recognise the phenotypic complexity of ADHD and acknowledge that it is a developmental disorder showing continuity and change in clinical presentation over time that is influenced by prenatal, biological and psychosocial environmental risk factors (see Fig. 1). Genes also appear to contribute to ADHD continuity and the development of antisocial behaviour in this disorder, and some of these genetic factors interact with environmental risk factors. However, risk factors for ADHD as a clinically defined disorder are not necessarily the same as those that influence its developmental course.

**CLINICAL IMPLICATIONS**

Understanding the aetiology and origins of ADHD, as with all psychiatric disorders, is important for paving the way to developing new and effective treatments (biological and non-biological) and for providing information and understanding to families and clinicians that in turn provides a framework for clinical management. Identifying genetic and environmental risk factors and examining how they co-act and interact to increase susceptibility to ADHD also provide a method of unpacking the heterogeneity of a clinically defined disorder in a meaningful way. This may lead to different ways of conceptualising the disorder and its diagnostic boundaries, and influence current methods of diagnostic classification.

In clinical practice some of the key goals are reducing symptoms, impairment and associated problems – notably antisocial behaviour in those already affected. Medication improves symptoms, but the long-term benefits for wider outcomes, including antisocial behaviour, are uncertain. Thus, additional risk reduction strategies aimed at reducing adverse outcomes are important (for example, this could involve reducing family conflict in those at highest genetic risk). Identifying both genetic and environmental risk factors that contribute to the course of the disorder is an important area of research activity so that the risk and protective pathways that lead to adverse outcomes and impairment can be elucidated. These types of research findings then provide an evidence base to inform the development of effective risk reduction strategies in the long-term management of ADHD. Intensive interventions for all children with ADHD is not pragmatic or necessarily desirable. Thus, identifying genetic and environmental risk factors as well as clinical characteristics that predict outcome can also be helpful in targeting resources and more carefully monitoring those who are at greatest risk of adverse consequences.

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