We have used a similar approach in the first set of analyses using the IMAGE stage I dataset of 680 families. Our aim in this study was to complete a systematic scan of genes that are functionally related to the main candidate gene systems identified to date. Our criteria for selection of candidate genes included analysis of genes with *a priori* evidence of association with ADHD and genes involved in the regulation of the neurotransmitter pathways implicated by the previous associations. We identified a total of 52 genes that fell into the categories of brain expressed catecholamine (dopamine, noradrenaline, serotonin) transporters, receptors, metabolism and catabolism genes. Additional categories included synaptic vesicle genes associated with synaptosomal associated protein gene (SNAP-25) and clock genes involved in regulation of circadian rhythms. In total we identified 1,536 SNPs with reported minor allele frequencies greater than 5% that fell within known functional sequences or tagged common haplotypes spanning each gene. Since some genes had a very high proportion of non-validated SNPs, we included 230 SNPs with non-validation status, of which only 13% turned out to be polymorphic. Of the 1,306 SNPs that were reported to be validated, only 68% were polymorphic in our sample, including 91% of 556 SNPs with genotypes available from Caucasian samples in the International HapMap database [13]; HapMap is an international resource for the selection of SNPs across the whole genome. Our final dataset included 928 polymorphic SNPs spanning 3,121 thousand bases pairs (kb) with an average SNP density of 1 every 3.36 kb. Despite the large sample size, we could only draw a few firm conclusions [17]. We found nominal significance with one or more genetic markers in eighteen genes, including the two most replicated findings in the literature: DRD4 and DAT1. Gene-wide tests adjusted for the number of markers studied in each gene identified associations with TPH2, ARRB2, SYP, DAT1, ADFRB2, HES1, MAOA and PNMT. Further studies will be needed to confirm or refute the observed associations.

Gene by environment interactions

To date most genetic studies in ADHD have focused on the detection of genetic variants that have a main effect on the risk for behavioural disorders. However, it has been recognized for a long time that gene-environment interactions are likely to play an important role on risk for behaviour and in some cases will be present in the absence of main effects. What is not widely understood is that the heritable component estimated from family, twin and adoption studies indexes both the main effects of genes plus the effects of gene-environment interaction. For this reason environmental research remains critical to our understanding of psychiatric disorders, even for those that are highly heritable such as ADHD.

An emerging literature on the effects of gene-environment interactions on behavioural disorders and an outline of the methodological issues has recently been reviewed [28]. Using a longitudinal population sample from Dunedin in New Zealand, Caspi, Moffitt and colleagues reported three key findings. First they hypothesized that a functional polymorphism in the promoter region of the gene encoding the neurotransmitter metabolizing enzyme monoamine oxidase A (MAOA), would moderate the effect of child maltreatment in the cycle of violence. Their results showed that maltreated children with genotypes that conferred low levels of MAOA expression were more likely to develop conduct disorder, antisocial personality disorder and adult violent criminal behaviour than children possessing high activity variants of MAOA [29]. In the second study they hypothesized that a functional variant in the promoter region of the serotonin transporter gene (HTTLPR) would moderate the influence of stressful life events on depression. They found that individuals with 1 or 2 copies of the HTTLPR short allele exhibited more depressive symptoms, diagnosable depression, and suicidality following stressful life events than individuals homozygous for the long allele [30]. This finding has been replicated in several further studies and is now one of the most consistent findings in psychiatric genetics [31-33]. In the third study they reported that a functional variant of the catechol-*O*-methyltransferase gene (*COMT* Val158Met) would moderate the risk of cannabis use by adolescents on the later development of psychosis in adult life [34].

These three findings highlight the importance of considering the effects of environmental exposure in the search for genetic risk factors. Moffitt, Caspi and Rutter noted several important methodological points in their review [28]. First, they noted that several of their initial reports were subsequently replicated, indicating the robust nature of some G × E interactions on human behaviour. Second, that in each case the environmental risk involved had shown an association with the disorder in previous epidemiological studies. In other words, they were known environmental pathogens. Third, in several of the reports it was noted that there was no main effect of gene alone. This has important implications since the search for genetic associations with behavioural disorders would have been unsuccessful in these examples if interaction with the environmental pathogen had not been taken into account. These findings have promoted a new wave of interest in gene-environment research, although identifying such interactions remains a major challenge. Unlike the DNA variation, where we know that we will soon be able to scan the entire human genome for associated genetic variants, environmental research will depend on careful selection of appropriate and measurable environmental risks. Information ascertainment on environmen-