worldwide. Recent review and meta-analyses of available data demonstrate an emerging set of findings that confirm prior hypotheses about the role of genetic variation within genes involved in the regulation of catecholamine neurotransmitters in susceptibility to ADHD [1,2]. Despite the importance of these findings, uncertainties remain due to the very small effect sizes that are observed, with average odds ratios in the range of 1.1 to 1.5. Under simple additive multi-gene models it is feasible that there exist numerous small genetic effects and we can estimate the contribution of the current loci to phenotypic variance (Table 1). Assuming an additive model, the variants identified so far explain around 3.3% of the variance, which is only 4% of the heritable component (assuming heritability for ADHD of 80%).

However, it is possible that the observed effects do not reflect the true strength of the associations and we have merely detected one or more pointers, behind which lie larger genetic effects. Further work is required to establish the true size of the genetic effects and to use genetic information to refine the clinical and neurocognitive phenotypes associated with the genetic markers. Underestimates of effect size can arise for several reasons and a number of difficulties exist in identifying associated genes and deriving accurate estimates of effect size using genetic association studies. Some of the most likely causes are listed in Table 2 and discussed in more detail below. So until we have performed further investigations we cannot be confident that the genes identified so far do not make a more substantial contribution. In the following sections we will consider the effects of linkage disequilibrium, allelic heterogeneity, population differences and gene by environment interactions.

Linkage disequilibrium and direct versus indirect association

Across small intervals of the genome (10,000 – 100,000 base pairs), a phenomenon called linkage disequilibrium (LD) is observed. LD is the non-random assortment of alleles at two distinct loci, meaning that the genotype at a second locus can be marginally predicted by the genotype at the first locus. This non-random assortment gives rise to marginal information about a second locus from the genotype of a first locus. So, the genetic markers reported to be associated with ADHD may not be the causal variants (functionally significant variants or FSVs), but rather nearby genetic markers that are tagging true causal variants through LD. The strength of association between tagging markers (usually single nucleotide polymorphisms or SNPs) and the causal variant is directly proportional to r^2 (the squared correlation between two markers), a common measure of LD [3]. Further information about LD and its uses and measures are available [4-6].

Direct association is the analysis of the functional allele, whereas indirect association is the analysis of a secondary allele garnering marginal signal by means of LD with the functional allele. For example, for the genes listed in Table 1 there is evidence that genetic variants associated with ADHD in the dopamine D4 receptor gene (DRD4) and the serotonin transporter promotor region (HTTLPR) may alter the expression or function of the genes (reviewed in Asherson et al., 2004 [2]). In contrast, the genetic variants within or close to the dopamine D5 receptor (DRD5), synaptosomal associated protein (SNAP-25), dopamine beta-hydroxylase (DBH) and serotonin IB receptor (5HT1B) genes are not thought to alter gene function themselves. Rather, the variants that have been genotyped are in LD with, and therefore tag, nearby functional genetic changes that do alter protein structure or expression. Analysis of the dopamine transporter gene (DAT1) is

Table 1: Average odds ratios and 95% confidence (CI) from the pooled analysis of genetic variants found to be associated with ADHD in more than one study (Faraone et al., 2005) [1]. Quantitative trait effects are estimated for these key findings using the variance components 2 relative risk calculator http://pngu.mgh.harvard.edu/~purcell/gpc/vc2rr.html. This program calculates the threshold, assuming a standard normal trait distribution, such that the QTL variance for the discrete category based upon this threshold would be the same as the QTL variance for the continuous measure. Assuming an additive genetic model, the proportion of phenotypic variance explained by the associated genes is around 3.2%. The number of families needed to replicate these findings with a nominal alpha of 0.05 and 80% is listed, in addition to the power from a sample of 200 families for the same significance level.

Gene	OR	95% CI		Allele frequency	QTL	Number of families to replicate with 80% power	Power in sample of 200 cases and 200 controls
DRD4	1.16	1.03	1.31	0.12	0.001	3196	0.115
DRD5	1.24	1.12	1.65	0.35	0.004	728	0.341
DAT1	1.13	1.03	1.24	0.73	0.001	2748	0.125
DBH	1.33	1.11	1.59	0.5	0.007	391	0.561
SNAP-25 (T1065G)	1.19	1.03	1.38	0.5	0.003	1043	0.253
SERT (HTTLPR)	1.31	1.09	1.59	0.6	0.006	466	0.490
HTR1B	1.44	1.14	1.83	0.71	0.010	315	0.652