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GUEST EDITORIAL

Attention deficit hyperactivity disorder: unravelling the molecular genetics

Attention deficit hyperactivity disorder (ADHD) is a clinically important, childhood onset condition that is characterised by marked inattention, overactivity and impulsiveness. There is evidence from family, twin and adoption studies that ADHD is familial[1] and highly heritable.[2] Molecular genetic studies are now underway and there have been a number of published findings, including three papers in this issue of *Molecular Psychiatry*.[3–5]

Current interest has focused on candidate genes involved in dopaminergic pathways. The rationale for this is largely based on the evidence that around 70% of children with ADHD show a rapid, symptomatic improvement with methylphenidate (Ritalin) which acts primarily on dopaminergic systems (see article in this issue of *Molecular Psychiatry*).[6] The most promising candidates so far are the dopamine transporter gene (DAT1) and the dopamine D4 receptor gene (DRD4). Findings for the DRD4 7-repeat allele and the 480-bp DAT1 allele have now been independently replicated.[4,5,7] These results are undoubtedly exciting yet judgement needs to be tempered with caution. Mixed findings are beginning to emerge and the story may be more complex than we anticipate.

DAT1 is an attractive candidate gene given that methylphenidate inhibits the dopamine transporter and that DAT1 knockout mice exhibit motor overactivity. In one of the first published reports, Cook *et al*,[8] using the haplotype relative risk (HRR) method found an association of the 480-bp DAT1 allele with ADHD in a sample of 49 children with DSM-III-R diagnosed ADHD and their parents.

The association with DAT1 has more recently been replicated in an Irish family-based study of 40 children with ADHD.[7]

The other group of studies has focused on the DRD4 7-repeat allele. Interest in DRD4 has been fuelled by suggestions of an association with higher novelty seeking scores.[9,10] Although findings have been mixed, novelty seeking is characterised by behaviors such as impulsiveness and excitability which are similar to symptoms of ADHD. Moreover DRD4 displays a high degree of variability that has been shown to be functionally significant. Earlier this year, Swanson *et al*[11] reported an association in a study of 52 probands with DSM-IV ADHD (combined type) and their parents. This study extended and replicated earlier positive findings from a case control study.[12] However the DAT1 findings were not replicated in this sample.

In this issue of *Molecular Psychiatry*, three other groups report findings on DRD4 and ADHD. Rowe *et al*,[4] use a case-control design and show a significant association with the DRD4 7-repeat allele and questionnaire-based categorical diagnoses of ADHD (combined and inattentive types) and dimensional measures of inattentive and hyperactive/impulsive symptoms. Results from the within-family analyses are more mixed in that there is some suggestion of linkage disequilibrium for inattentive symptoms but not for any categorical definition of ADHD. The study by Smalley *et al*[5] is based on a larger sample of 133 multiplex families of children with DSM-III-R/DSM-IV diagnosed ADHD. Using the TDT, again there is evidence of linkage disequilibrium with the DRD4 7-repeat allele which confers a 1.5-fold increased risk for ADHD. However the results of linkage analysis in the 84 affected sibling pairs are less conclusive. These two studies provide independent replications of Swanson *et al*'s[11] findings. However results from the analyses of the family-based data of Rowe *et al*[4] and the affected sib pair data of Smalley *et al*[5] are mixed. In this same issue, Castellanos *et al*[3] who use a case-control design and include 41 children with severe ADHD, are unable to obtain a positive association with the DRD4 7-repeat allele even when comorbidity and ethnicity are taken into account. Moreover they find that within the patient group, the presence of the DRD4 7-repeat allele is not associated with clinical symptom severity or brain morphometric differences.

The results emerging from molecular genetic studies of ADHD are important and interesting in that there have been independent replication studies showing associations with DAT1 and DRD4. Nevertheless, effect sizes appear to be small and these positive findings are also accompanied by reports of apparent non replication. It is improbable that the molecular genetic basis of ADHD will be any easier to unravel than for other psychiatric disorders and thus, at present, it seems wise to remain cautious in drawing conclusions.

A striking feature highlighted in all of these issues is the problem of sample homogeneity. First there is

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the issue of how best to define ADHD. In the UK, ICD-10 criteria for 'hyperkinetic disorder' require symptoms of inattention *and* hyperactivity *and* impulsivity in more than one setting and thus define a more severe disorder. To fulfil DSM-IV criteria for ADHD-combined type, symptoms are required in two areas, that is inattention *and* hyperactivity/impulsiveness. However DSM-IV also allows for defining inattentive and hyperactive/impulsive types which only require symptoms from one of these symptom groups. However different studies have used a variety of ascertainment procedures and different diagnostic and inclusion criteria. Samples are thus likely to differ in terms of symptom severity as well as comorbidity and it is difficult to ascertain how important a part these differences are likely to play. Thus for the positive reports of association with DRD4, in the Swanson[11] study, the sample consisted of methylphenidate-responsive, DSM-IV ADHD-combined type cases and serious comorbidity was excluded. In the replication studies reported in this issue of *Molecular Psychiatry*, one sample[5] included DSM-III-R or DSM-IV cases of ADHD with substantial rates of comorbidity and in the other,[4] DSM-IV ADHD was defined using questionnaire reports which yield a broader definition than interview-diagnosed clinical disorder. Castellanos *et al*[3] point out that their failure to replicate may be accounted for by sample differences in that their study included cases with severe ADHD and a high rate of comorbidity.

Second, in common with molecular genetics research for other psychiatric disorders, there are additional problems of ascertainment differences in terms of observable demographic and clinical factors such as ethnicity, sex, age and IQ.

Third, for the case-control association studies, there is the problem of population stratification. Although the replicated DAT1 results are based on studies using the HRR method,[7,8] the mixed DRD4 findings are based on studies using case control[3,4,12] as well as family-based designs.[4,5,11]

Finally the most obvious problem of all is the issue of power. It has been highlighted that association studies where there is a failure to replicate need to be interpreted with care.[13] For example, for DAT1, a case control sample of at least 75 cases would be required to have sufficient power (80% power, $\alpha = 0.05$) to detect the effect size reported in the positive study by Gill *et al*[7] (odds ratio = 2.86). Similarly a sample size of at least 175 would be required to detect the effect size for DRD4 reported in the positive study by Swanson *et al*[11] (odds ratio = 2.07). So far reported results from association studies of ADHD have been based on small sample sizes. Thus apparent non-replication or negative findings may be due to a lack of statistical power. Linkage studies require even larger samples to detect susceptibility genes of small-moderate effect size. This is illustrated in the paper by Smalley *et al*,[5] where statistically significant findings for DRD4 could be detected using the TDT but not by examining the rate of IBD sharing in the affected sib pairs. A further difficulty is that when samples are subdivided for example on the basis of the presence/absence of comorbidity and different clinical subtypes, the size of each group becomes even smaller. Inevitably larger studies, pooling of samples and meta-analyses[13] are going to be required. This would improve confidence in our ability to detect susceptibility genes of modest effect and also enable us to generate samples which at least appear to be clinically and demographically homogeneous. Moreover, so far published work has focused on candidate genes. Even in studies where positive associations have been found, DRD4 and DAT1 account for only part of the genetic contribution to ADHD and clearly whole genome searches are required. Even larger samples will be needed as we look ahead to the time when whole genome association studies are carried out.

This is an exciting time for molecular genetics research of ADHD and initial results look promising. However unravelling the molecular genetic basis of ADHD has only just started and further results are awaited with interest.

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