Genome-wide association scan of attention deficit hyperactivity disorder

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Editorial

Perspective on the Genetics of Attention Deficit/ Hyperactivity Disorder

Benjamin M. Neale[1,2,3,4] and Stephen V. Faraone[2,5]*

[1]*Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College, London, UK*
[2]*Department of Psychiatry, SUNY Upstate Medical University, Syracuse, New York*
[3]*Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts*
[4]*The Broad Institute of Harvard and MIT, Cambridge, Massachusetts*
[5]*Department of Neuroscience, SUNY Upstate Medical University, Syracuse, New York*

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This special issue of Neuropsychiatric Genetics presents both a comprehensive overview of and the latest progress in the genetics of Attention Deficit/Hyperactivity Disorder (ADHD). In many ways, this issue's wide range of topics reflects how genetics and our understanding of ADHD have developed over the course of the last 25 years. This issue includes the phenotypic interrogation of ADHD in families to assess heritability and the suitability of measures; linkage analysis of clinical and quantitative phenotypes; candidate gene association studies of biologically relevant hypotheses; genetic analyses of endophenotypes and comorbid disorders; gene expression in an animal model of ADHD; and, finally, a sequence of articles describing the genome-wide association scan (GWAS) from the International Multi-site ADHD Gene (IMAGE) Project. This set of articles recapitulates the major trends in the field of complex psychiatric genetics, underscoring how genetic studies of ADHD have evolved, and what approaches are needed to uncover the genetic etiology.

Among the common psychiatric diseases, ADHD is one of the most common (~8–12% worldwide) and has one of the highest heritabilities, with estimates from twin studies averaging around ~75% [Faraone et al., 2003, 2005]. The drugs that treat ADHD are highly efficacious [Faraone et al., 2006], making ADHD one of the most treatable psychiatric disorders. The efficacy of these treatments has promoted theories postulating dysregulation of catecholaminergic synapses as central to the etiology of the disorder [Biederman and Faraone, 2005]. Despite the high efficacy of ADHD medications, these treatments remain palliative, not curative, leaving patients with much residual disability. One hope for genetic studies is the potential for the discovery of new biological pathways and new targets for treatment.

The candidate gene associations presented in this special issue highlight the difficulty researchers have had in consistently replicating association findings. Many of the candidate genes proposed for ADHD have strong biological narratives and extensive prior association results. Surveys of this literature show that some DNA variants are conclusively negative [Cheuk and Wong, 2006] and others have withstood the test of meta-analysis across multiple studies [Mick and Faraone, 2008]. But are these latter findings convincingly significant? As it stands now, none of these associations meet the significance threshold of genome-wide association of $P < 5 \times 10^{-8}$ [Dudbridge and Gusnanto, 2008; Pe'er et al., 2008]. These associations are therefore not conclusively significant, but may still be relevant to ADHD.

In the broader genetics literature, a great deal of work has been published on the difficulty of confirming candidate gene associations. Potential explanations include lack of power; false positives; publication bias/ "file drawer" problem; phenotypic heterogeneity, and genetic heterogeneity [Hirschhorn and Altshuler, 2002; Colhoun et al., 2003; Lohmueller et al., 2003; Redden and Allison, 2003; Munafo et al., 2004; Neale and Sham, 2004]. How these issues apply to ADHD remains to be seen, but in all likelihood, each of these specific explanations is going to be somewhat responsible for ambiguities in the ADHD genetics literature. Publication bias (i.e., it is easier to publish a significant finding than a nonsignificant one) is almost certainly culpable for some inflation in the number of "significant" findings in the literature, but has little impact on study design. Other issues are inherently intractable, and as such are difficult to solve through the application of different techniques or study designs. For example, if genetic heterogeneity gives rise to completely indistinguishable phenotypes, no increase in the precision of phenotypic assignment will resolve this problem and improve power. The consistent heritability findings given a range of ADHD definitions suggest some amount of robustness in the genetic underpinnings of the phenotype.

Historically, the heritability and quantitative models of phenotypes provided strong evidence for a genetic contribution to variation in the population with respect to ADHD. Consequently, genetic linkage analysis, which correlates genetic sharing with phenotypic information in families, was applied extensively to ADHD. Faraone et al. [2008] present another linkage analysis of ADHD, yielding no significantly linked regions. Zhou et al. [in press] have applied a meta-analysis technique to linkage results to determine whether there are any consistently implicated regions yielding 16q23.1 as a significantly linked region. In addition to ADHD diagnosis, Doyle et al. [in press] present a linkage scan on neuropsychological phenotypes related to ADHD. Such work may enable the identification of risk factors more closely associated with the biological underpinnings of ADHD.

This issue presents a sequence of articles analyzing the first genome-wide association study of ADHD. This study is based on the aforementioned IMAGE dataset. The genomic coverage of this set of articles is dramatically improved compared with

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*Correspondence to: Stephen V. Faraone, Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, 750 East Adams St., Syracuse, NY 13210.
E-mail: faraones@upstate.edu

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all previous efforts to identify the genetic predisposition to ADHD through association analysis. Our primary analysis applied the transmission disequilibrium test to 909 trios [Neale et al., 2008]. None of these assayed SNPs crossed the conservatively defined genome-wide association threshold we have adopted of 5×10^{-8}. This threshold is built on the principle that if we genotyped all common variation (MAF > 5%) in the human genome, then the effective number of tests is estimated at about one million independent tests, given the linkage disequilibrium in the human genome [Dudbridge and Gusnanto, 2008; Pe'er et al., 2008]. We consider this work the primary report and consequently will be used for meta-analysis when other ADHD GWAS data sets become available.

In addition to our main analysis, we present a series of secondary analyses attempting to mine the dataset more thoroughly. This work is much more explicitly hypothesis-generating with the aim of insulating against additional multiple testing burden. These articles highlight ways to use phenotypic and environmental data to potentially increase the power to detect associations.

Lasky-Su et al. [2008] apply family based association test (FBAT) methods to the inattentive and hyperactive-impulsive symptom dimensions of ADHD. The potential of this approach was initially suggested by the twin study of Gjone et al. [1996], which applied a mathematical model to determine if the heritability of attention problems increased with their severity. This model is useful because one might expect cases at the severe end of the dimension to have a categorical disorder such as ADHD. If ADHD accounted for the heritability of attention problems we would see increasing heritability with increasing severity. However, heritability did not change with severity, so the authors concluded that there was, in the population, a continuously distributed dimension of genetic liability to attention problems. Similar findings were reported by Levy et al. [1997] and Willcutt et al. [2000]. Thus, available data support the idea that ADHD can be viewed as the extreme expression of a trait that varies quantitatively in the population. This, in turn, suggests that QTL linkage analysis using quantitative measures of ADHD expression provides a powerful strategy to discover genes for ADHD.

Using the PBAT screening algorithm, two SNPs met genome-wide significance within a phenotype but not across all phenotypes tested. The investigators analysis of age at onset also found no genome-wide significant evidence [Lasky-Su et al., in press].

Sonuga-Barke et al. [2008] present a gene-by-environment ($G \times E$) analysis of the genome-wide association dataset. Utilizing measures of Conduct Disorder (CD), maternal warmth, and expressed emotionality, a modified version of the family based association test proposed by Vansteelandt et al. [2008] was implemented to test for $G \times E$. $G \times E$ analyses may enable the partitioning of genetic liability to disease into more homogenous groups. As such, greater power to detect association may potentially be achieved through the use of the models. None of the SNPs tested achieved genome-wide significance on the main effect of the moderator or the test for the interaction between the moderator and ADHD diagnosis.

The relationship between CD and ADHD is still unclear from a phenotypic level. Contrasting hypotheses in the literature include the perspective that a diagnosis of ADHD and CD represents a more extreme form of ADHD or is a different disorder altogether from ADHD alone. Similarly, the quantitative measures of ADHD in the probands may identify severity risk factors. Such work, however, is complicated by the presence of medication effects and rater bias, both of which are known to affect the quality of measurement of quantitative measures of ADHD. These results are useful for the design of a targeted association follow-up project, rather than the strong formation of biological hypotheses.

Anney et al. [2008] present a perspective on the some of the difficulties of genotyping calling using the SNP chip technologies (e.g., Affymetrix, Illumina, and Perlegen). These SNP chips convert quantitative measurements of intensity into discrete genotype calls. Such analyses are fraught with difficulties ranging from structural variation (e.g., copy number variable regions) to technical artifacts and biases. Using the IMAGE–Perlegen GWAS data, the different varieties of cluster plots are presented. Additionally, the effects of nonrandom missingness on the Hardy–Weinberg deviation test are explored, as a key to the detection of SNP genotyping errors. The difficulties presented in this article only serve to highlight the importance of proper quality control in the context of genome-wide association.

Continuing the genome-wide association theme, but drawing on a different dataset, Mick et al. [2008] present the results from a pharmacogenetics scan of ADHD and the methylphenidate transdermal system. Capitalizing on a clinical trial, with genetic data available, the authors attempt to identify genetic variation underpinning the response to methylphenidate as administered through a patch. None of the markers tested showed genome-wide significant association, indicating that this endophenotype of drug response did not sufficiently reduce the genetic complexity to identify risk factors for ADHD. However, the sample size for this study was small (N = 309), and so the power to detect association is considerably lower than that of the genome-wide association scan of ADHD presented from IMAGE.

In summary, the articles in this issue show how genetic studies of ADHD have taken great strides toward discovering genetic variation predisposing to the disorder. The results of many linkage studies show with certainty that the individual effects of ADHD susceptibility genes cannot be large. Given that the IMAGE GWAS study was powered to detect genotypic relative risks greater that 1.3, we now know that the individual effects of ADHD susceptibility genes must beneath this threshold. This, in turn, implies that low power is the most likely explanation for the lack of definitive genetic findings. As the complexity of the genetic architecture increases (many smaller effects, epistasis, gene–environment interaction, dominance, etc.), then the power to detect association decreases. Other complex traits, such as diabetes, bipolar disorder, and Crohn's disease, required sample sizes on the order of 2,000–5,000 cases with similar number of controls to identify the first replicable associations [Altshuler and Daly, 2007; Parkes et al., 2007; Rioux et al., 2007; Saxena et al., 2007; Scott et al., 2007; Sladek et al., 2007; Steinthorsdottir et al., 2007; Zeggini et al., 2007; Ferreira et al., 2008]. The GWAS of bipolar disorder, for example, leveraged a sizeable chunk of the existing ascertained samples with DNA collected, yet only found genome-wide significant evidence implicating two genes [Ferreira et al., 2008]. Although the findings are welcome, these genes only account for a small fraction of the disorder, suggesting further ascertainment is necessary for uncovering further variation.

As a field, ADHD has the good fortune of having several thousand samples collected worldwide, with collaborative efforts supported by the grant R13MH59126 from the National Institute of Mental Health. Investigators with ADHD GWAS datasets are also participating in the Psychiatric GWAS Consortium (PGC), a confederation of 101 scientists from 11 countries and 48 institutions having GWAS data sets on ADHD, autism, bipolar disorder, schizophrenia, and major depression. The PGC investigators have agreed to participate in coordinated mega-analyses both within and across disorders.

Our capacity to assay the genome has implications for statistical power. If we can only capture 0.1% of the common variation in the human genome, then the chances that we genotype a variant related to ADHD is low, even if the selection

is biologically informed. Thus, poor coverage of the genome implies low power to detect association. Fortunately, technological developments have changed the landscape of coverage. The advent of genome-wide association SNP arrays enables us to examine ever -greater numbers of common variants in the human genome.

Despite these considerations, this issue heralds the dawn of the age of genome-wide association for the identification of genetic risks to ADHD. The articles presented here are simply the first step, rather than the final word on the genetics of ADHD. They have already motivated the collection of additional ADHD GWAS datasets. These datasets promise to provide further understanding of the likely genetic architecture of ADHD, how large these effects can possibly be, and the extent to which heterogeneity is inhibiting our capacity to understand ADHD at a neurobiological level.

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