Meeting Report

Report From the Third International Meeting of the Attention-Deficit Hyperactivity Disorder Molecular Genetics Network

The ADHD Molecular Genetics Network

Growing evidence of a genetic contribution to attention-deficit hyperactivity disorder (ADHD) has prompted investigators from around the world to convene annually to discuss ways of facilitating collaboration and sharing information about their work on this topic. The number of participants in the meeting has grown each year as a result of enthusiastic responses to each previous conference. This third annual meeting, held in Boston, began with presentations of ongoing and proposed collaborations. The status of Hypescheme, an operational criteria checklist developed in an effort to promote the reliable communication of information related to ADHD, was reviewed. A symposium was conducted to review current evidence for whether DSM-IV subtypes breed true. Finally, new data from individual research sites were presented. Despite recent advances, more work is needed to better characterize heritable aspects of the ADHD phenotype as well as the actual candidate genes themselves.

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INTRODUCTION

Converging findings from twin and adoption studies suggest that attention-deficit hyperactivity disorder (ADHD) has a substantial genetic component [Faraone and Doyle, 2001]. Recently, technological and statistical advances in the field of molecular genetics have allowed researchers to move beyond the quantification of heritability to begin to identify specific genes that are associated with the ADHD phenotype. Because animal models, theoretical considerations, and the effectiveness of stimulant treatment implicate dopaminergic dysfunction in the pathophysiology of ADHD, the first molecular genetic studies of ADHD have targeted genes in the dopamine pathway [Swanson et al., 2000]. Since the mid-1990s, case control and family-based association studies have identified several such genes that may mediate susceptibility to ADHD [Faraone and Biederman, 1998], including the dopamine transporter (DAT1) and dopamine receptor D2 (DRD2), D4 (DRD4), and D5 (DRD5) genes, dopamine beta hydroxylase (DBH), and catechol-o-methyl transferase (COMT). However, failures to replicate findings, the complexity of the ADHD phenotype, the likelihood of genetic heterogeneity, and the probability that several genes of small effect are acting in concert indicate that there is much work to do before the genetic mechanisms that contribute to ADHD are fully understood.

Clarifying the genetic architecture of complex phenotypes such as ADHD appears to require large samples and collaborative efforts. Experience with studies of schizophrenia, bipolar disorder, and autism shows that the sample sizes collected by individual investigators may be adequate to provide weak evidence for linkage but are not sufficient to find significant evidence or to clone disease genes. Such considerations have prompted researchers studying or planning to study the molecular genetics of ADHD to form the ADHD Molecular Genetics Network [Faraone, 2001]. Thus far, three annual meetings of the Network, supported by grants from the National Institute of Mental Health and the Shire-Richwood Educational Foundation, have taken place. In 1999, the first annual conference discussed ways to increase communication among researchers, the feasibility of using common measures across sites, and strategies for defining genetically useful phenotypes [ADHD Molecular Genetics Network, 2000]. In 2000, the second conference...
included a detailed presentation and evaluation of Hypescheme, an operational criteria checklist developed to promote communication of information relevant to ADHD, as well as discussions of continued challenges to collaboration and joint data analyses, a new ADHD-specific rating scale (the SWAN) developed for genetic analyses, and proposed collaborative projects [Paratore, 2001]. This article reports the proceedings of the Network’s third annual international conference, held in Boston on 9 June 2001.

ONGOING AND PROPOSED COLLABORATIONS

Two projects initially proposed during the second annual ADHD Molecular Genetics Network meeting are currently in progress. Dr. Richard Todd is conducting a joint analysis of the ADHD phenotype and genotype using a latent class analysis (LCA) approach to phenotype definition. The intent of this project is to replicate and extend existing latent class categorizations of the ADHD phenotype and to test whether one or more of these latent classes is associated with DAT and/or DRD4 alleles. Additionally, Dr. Todd plans to incorporate both phenotypic and allelic data to derive genotype-based phenotypes in multisite data. The heritability of these phenotypes will subsequently be examined in family and twin samples.

Dr. Irwin Waldman is organizing a collaborative project examining interactive versus additive effects of DAT1 and DRD4 on ADHD diagnoses and symptom dimensions. The proposed study aims to answer the question of whether DAT1 and DRD4 act additively to increase the risk for ADHD, or whether they interact in some fashion. Such an interaction could occur synergistically, such that the action of one gene is enhanced by the other, or via an alternative pathway model, which predicts two alternative, genetically based forms of ADHD, one predisposed to by DAT1 and the other predisposed to by DRD4. Information required in order to collaborate in these projects was circulated via e-mail.

Dr. Todd also made a general appeal for collaborative studies that illuminate the heritable aspects of the ADHD phenotype via comorbidity, symptom dimensions, statistical techniques, or other methods. Although twin studies have consistently produced high levels of heritability with regard to DSM-III-R– and DSM-IV–based definitions of ADHD, high levels of heritability alone do not directly translate into straightforward strategies for detecting genes. Genetically similar cases must be included in samples in order for successful replications of linkage and association studies to occur. If only certain aspects of the ADHD phenotype are heritable, or if categorical/continual definitions or different symptom dimensions of ADHD capture genetically dissimilar entities, including such genetically heterogeneous constructs in single samples will hinder our ability to identify or replicate key risk alleles. There was widespread agreement that attention to phenotypic complexity is paramount.

Several participants underscored the need to attend to the complexities of the genotypes under investigation. For example, the 48 bp VNTR in exon III is the most commonly studied polymorphism related to DRD4 that has been examined in studies of ADHD. The 7-repeat variant has attracted attention because a meta-analysis shows it is associated with ADHD [Paratore et al., 2001] and because it leads to in vitro functional changes in gene expression [Van Tol et al., 1992]. But the relevance of these in vitro changes is not clear and other areas of the DRD4 gene have not been systematically studied. For example, researchers from Toronto’s Hospital for Sick Children are currently examining whether a DNA variant that is in linkage disequilibrium (LD) with the 7-repeat allele is contributing to the ADHD phenotype. Barr et al. [2001] found that one haplotype containing a 4-repeat allele was not transmitted to affected probands more often than expected by chance. Although this finding raises the question of certain haplotypes serving a protective function, firm conclusions about this issue cannot be made until replications are undertaken. Nonetheless, such findings serve as an example of the need to explore the molecular complexities of candidate genes in the dopamine system. The point was also made that without a more detailed understanding of candidate genes themselves, a fine-tuned dissection of aspects of the ADHD phenotype that are associated with the 7-repeat allele of DRD4 may be premature.

HYPESHEME UPDATE

When the ADHD Molecular Genetics Network first met in 1999, it was clear that the lack of a standard assessment battery across research groups posed a significant challenge to multisite collaborations. Many participants were in favor of adopting a method for pooling data based on the underlying constructs of interest, rather than specific assessment measures. Such a method was, at that time, already under development by Curran et al. [2000]. As part of the 2000 meeting, these investigators presented a completed draft of their data-pooling measure, called Hypescheme, to Network members who wished to attend a training session.

Hypescheme contains both DSM-IV and ICD-10 diagnostic criteria for ADHD as well as information regarding comorbid psychiatric and developmental disorders. It is intended to be a final common checklist that can be completed by experienced clinicians/researchers using all of the data that are available to them. Potential data sources include structured interviews, behavior rating scales, behavior observations, and case notes. Because Hypescheme contains the inattention, hyperactivity, and impulsivity items necessary for making DSM-IV and ICD-10 diagnoses of ADHD and hyperkinetic disorder, it may facilitate the exchange of information across sites on an item level as well as a diagnostic level. Additional information required for these diagnostic systems is also assessed, such as age at onset and different situations in which impairment occurs. Symptoms for DSM-IV and ICD-10 oppositional
defiant disorder and conduct disorder are also coded at the item level. Other comorbid psychiatric disorders, as well as neurological and developmental disorders, are coded as summary items only.

At the 2001 meeting, Dr. Sarah Curran reported the present status of Hypescheme. At present, there are 31 registered users of the system. Problems that have been identified include difficulty with screen size, combining data from different computers, and printing out the summary diagnostic information. Currently, a revision of Hypescheme is in process. The revision will address these difficulties and will also fill in information gaps that have been highlighted by users. Additional features to be included are fields for chronic motor tics, birth weight, whether a subject was part of a twin or multiple birth, and questions about maternal alcohol abuse during pregnancy. Additionally, the authors of Hypescheme plan to add questions regarding the adequacy and outcome of a trial of methylphenidate. When participants were asked about obstacles to their involvement in Hypescheme, researchers from various sites expressed concern about the time commitment required to transfer data to the Hypescheme format. The possibility of obtaining NIH funding for this process was discussed with general agreement that such a project should go forth.

Discussion turned to whether the Hypescheme section on medication should be expanded. The majority of conference participants were in favor of including a detailed section about medication response, including expanded medication options (e.g., tricyclic antidepressants, guanfacine) and information about dose and response. Currently, a significant number of research sites have collected detailed data on drug response for pharmacogenomic studies. Several other sites are now in the planning process of clinical trials and expressed an interest in measuring drug response in a comprehensive fashion. Measures such as the Clinical Global Impressions (CGI) scale, ADHD rating scale, and stimulant side effect scale were discussed. The point was made that symptom ratings do not address the issue of wellness as well as the CGI. Nevertheless, several researchers questioned the adequacy of the CGI as a measure of drug response. In the end, there was consensus that interest in pharmacogenomics is high within the ADHD Molecular Genetics Network as well as the scientific community at large. Participants saw the need for more time to propose and decide on a core set of questions about medication response. It was suggested that such a discussion happen over e-mail.

**DRD5: THE CASE FOR A COLLABORATION**

To explore the dopamine hypothesis of ADHD further, Dr. Aiveen Kirley made a case for studying the association between the dopamine D5 receptor (DRD5). DRD5 maps to specific limbic regions and is located on chromosome 4. The human genome also contains at least two DRD5 pseudogenes on chromosomes 1 and 2 [Nguyen et al., 1991]. Dr. Kirley presented a brief literature review of studies that have found associations [Daly et al., 1999] and trends toward associations [Tahir et al., 2000; Payton et al., 2001] between DRD5 and ADHD symptomatology. DRD5 has also been associated with conditions that are commonly comorbid with ADHD such as antisocial behavior [Vanyukov et al., 2000] and substance abuse [Vanyukov et al., 1998]. There was a general consensus that a collaborative study of DRD5 would be a worthwhile endeavor, with the suggestion to look at multiple polymorphisms at the same time in order to be cost-effective.

**COORDINATED GENOTYPING NETWORK**

Dr. Richard Ebstein led a discussion about the possibility of seeking funding for a coordinated genotyping network for molecular genetic studies of ADHD. Dr. Ebstein pointed out that DRD5 is just one example of a potentially interesting susceptibility gene to explore with regard to ADHD. Citing Zubenko [2000], he highlighted the possibility that certain risk alleles have pleiotropic effects and are shared across multiple neuropsychiatric conditions. For example, autism and language disorder may share an association with chromosome 7q [Folstein and Mankoski, 2000]. ADHD researchers may wish to take advantage of linkage disequilibrium (LD) to map genes at chromosomal hot spots identified in studies of other major mental illness. Reich et al. [2001] have provided evidence that LD typically extends 60 kb from common alleles in a U.S. population of north European decent, thereby suggesting that LD mapping is feasible in such samples.

Funding for a coordinated genotyping network would be used to create comparable cross-site data sets using Hypescheme, to prioritize candidate genes, to choose polymorphisms for genotyping, and to genotype these polymorphisms using a cost-effective strategy that capitalizes on the large number of samples available through the network. Dr. Ebstein gave an example of genotyping a subset of the data to see if there is any evidence of a signal and then genotyping the remainder of the sample to validate the initial finding. Having a genotyping resource of triads would be cost-efficient because it would reduce the need to do further recruiting of samples as potential susceptibility loci are identified. Promising areas to target include chromosomes 6 and 7 on which potential genes for dyslexia have been identified. Many triad samples are now available and groups are continuing to collect data. Indeed, a resource for collecting and storing genotypic information is a logical corollary to Hypescheme and its detailed phenotypic information.

Participants agreed that a coordinated genotyping network would be useful. The idea of examining “candidate genes” implicated in other disorders was seen as potentially useful given the high rates of comorbidity in ADHD, but some concern was expressed that prior findings in other disorders would not be precise enough to be of use for ADHD. It was agreed that, at this exploratory stage, an e-mail discussion of the aims of the coordinated genotyping network will occur. Once such aims are in place, interested participants could explore specific plans for achieving them.
Issues to discuss include how to protect/share the data from such a triad repository and how to set priorities for chromosomal regions to be studied.

SYMPOSIUM: DO DSM-IV SUBTYPES BREED TRUE?

Although DSM-IV subtypes have clinical implications, the extent to which they are useful for genetic studies has been unclear. Specifically, it is not known whether these subtypes have distinct or shared familial etiologies. Five researchers have examined the issue of whether specific subtypes breed true, i.e., whether a specific subtype in a proband predicts that subtype in a relative. Results were mixed. Based on data from families participating in the population-based Australian twin study, Dr. David Hay and colleagues found evidence to suggest that DSM-IV subtypes do breed true, with no evidence of a gender effect [Levy et al., 1997]. Similarly, in his sample of twins from Missouri, Dr. Richard Todd and colleagues found that distinct latent classes, which overlap significantly with DSM-IV subtypes, appear to be transmitted between relatives [Hudziak et al., 1998]. In contrast, the remaining studies did not support this hypothesis. In a Colorado twin study in which at least one twin showed evidence of reading problems, Willcutt et al. [2000] found that extreme hyperactivity/impulsivity may be attributable to different etiological influences in individuals with and without extreme inattention. Smalley et al. [2000] found no familial clustering of subtypes in their study of affected sibling pairs. Similarly, in a clinically ascertained sample selected based on a single affected child, Faraone et al. [2000] found that the inattentive and combined subtypes did not breed true, although the hyperactive-impulsive type of the disorder was found almost exclusively among relatives of hyperactive-impulsive probands. Taken together, these studies do not allow for firm conclusions about whether DSM-IV subtypes represent distinct familial conditions. They do suggest that there may be fundamental differences between population samples (which were ascertained in the twin studies) and clinical samples (which were ascertained by the family studies). Differences between these types of samples could be due to the relative low prevalence of inattentive ADHD in clinics compared with the population. Participants also noted that phenotypic differences between subtypes were sometimes small because the presence or absence of a single symptom could change the diagnosis from one subtype to another. There was general agreement that although the DSM-IV subtypes may be useful in clinical practice, research should focus on defining subtypes that would be useful for molecular genetic studies.

DATA PRESENTATIONS

Presentations of data collected from individual research sites were made by Drs. Irwin Waldman, Sarah Curran, Jon Mill, Luis Augusto Rhode, Keith McBurnett, Emma Van der Meulen, Jim Swanson, Sue Smalley, Cathy Barr, Tom Price, Philip Asherson, and Ziarah Hawi. These data will be published separately and will not be reviewed here.

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APPENDIX


REFERENCES


Faraone


