

## Genetics of Childhood Disorders: XXI. ADHD, Part 5: A Behavioral Genetic Perspective

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*We believe that a valid classification is an essential step in science. In medicine, and hence in psychiatry, classification is diagnosis.*

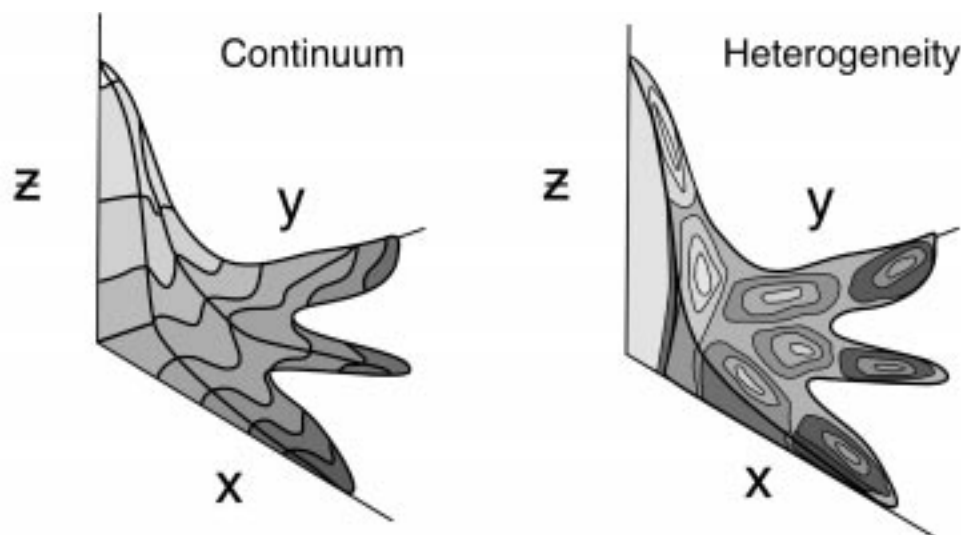
—Robins and Guze, 1970, p. 107

As conceptualized in *DSM-IV*, attention-deficit/hyperactivity disorder (ADHD) is a common syndrome of childhood characterized by problems of inattention and/or hyperactive-impulsive behavior that is frequently associated with comorbid psychiatric conditions and educational or vocational failure. The prevalence of ADHD is estimated to be between 3% and 9% in children and several-fold higher in boys. These prevalence estimates and recent prescription patterns for stimulant medications have led to controversies in the lay press regarding possible overdiagnosis and overtreatment of ADHD.

The results of modern twin studies suggest that much of the controversy surrounding the supposed epidemic of ADHD is secondary to fundamental misconceptualizations about its nature. Notwithstanding the tremendous advances in treatment and research that have been made possible by the adoption of a

standard diagnostic nomenclature, the *DSM* approach is categorical. In contrast, the results of several population-based twin studies from around the world are most compatible with ADHD representing the extreme of one or more continua of problems with inattention and hyperactivity-impulsivity (for example, Levy et al., 1997). If correct, ADHD is akin to common medical conditions such as hypertension or diabetes in that the criteria for defining who is ill represent an arbitrary cut-off along a continuum of blood pressure or serum glucose level, respectively. The definition of a case, then, becomes entwined with the efficacy of our treatment approaches, whether pharmacological or behavioral. The conceptualization of ADHD as a quantitative trait is in keeping with the noncategorical tradition such as represented by the Attention Problems (AP) scale of Achenbach (1977).

Whether viewed as a discrete disorder or as a quantitative trait, estimates of the heritability of ADHD are uniformly high (reviewed by Faraone and Biederman, 1998; Todd, 2000).



**Fig. 1** Two general models illustrate how both continuum and multiple heterogeneity genetic models can explain the distribution of symptoms for a disorder in the general population. For the case of attention-deficit/hyperactivity disorder, the axes might be defined as  $Z$  = prevalence,  $X$  = inattentive symptoms, and  $Y$  = hyperactive-impulsive symptoms. The continuum model resembles a lava flow, where there are smooth transitions in genetic risk to the extreme *DSM-IV* subtypes (represented by the 3 dark-colored ends of the distributions). For the heterogeneity model, the same distribution resembles a piece of cloisonné in which distinct genetic risk factors contribute to different parts of the observed distribution of phenotypes.

It is unclear whether the same basic heritable elements predispose to the presence of problems with attention, hyperactivity, and impulsivity or whether unique genetic elements contribute to each problem area. Similarly, it is unclear whether the presence of comorbid psychiatric problems or learning difficulties is due to pleiotropic genes that may result in different disorders, to coheritability of genetic elements predisposing to different problem areas, or to other mechanisms such as environmental effects or assortative mating among parents.

Which children are seen in our clinics is determined by complex referral patterns. Hence, clinically based studies of ADHD have potential biases, particularly regarding comorbidity. School-based studies overcome some of these difficulties, but they exclude individuals who are not in school. The most severely affected cases, and perhaps the most interesting from a genetic point of view, are thereby undersampled.

A complementary approach that may overcome some of these difficulties is to sample individuals from birth records. Though not without possible shortcomings, birth records-based twin studies have the advantage of sampling the entire spectrum of possibly affected individuals using genetically informative designs. Coupled with analytic approaches that are agnostic regarding the nature of the disorder or the mechanisms of comorbidity, such population-based twin studies offer a powerful approach to resolving these issues. We are in the process of collecting data from such a birth records-based twin sample from the state of Missouri (Hudziak et al., 1998, 2000). Our initial results from this study suggest that ADHD is underdiagnosed, has complex mechanisms of comorbidity, and is genetically heterogeneous.

Our basic approach has been to collect full *DSM-IV* symptom information on all twins irrespective of whether or not they qualify for a diagnosis. Using a categorical version of traditional factor analysis called latent class analysis (McCutcheon, 1987), we subdivide the population sample of twins into mutually exclusive classes based on twin or parent report of *DSM* symptoms. Defining topologies of phenotypes in this manner has the advantage that information about the occurrence of symptom clusters from different diagnostic domains is extracted without previous conceptualizations of diagnostic boundaries or patterns of comorbidity. A latent class approach also naturally tests whether the derived classes represent distinct entities or points along a continuum of severity. It should be emphasized that as with all statistical approaches, the results of any latent class analysis are dependent on the quality of the data analyzed, the sample size, and the underlying reality of nature.

Our currently published work is compatible with the presence of 2 latent classes which identify 2 of the 3 *DSM-IV* ADHD subtypes: primarily inattentive and a combined inattentive/hyperactive-impulsive subtype (Hudziak et al., 1998; Neuman et al., 1999). The majority of individuals in these subclasses qualify for a diagnosis of ADHD. Classes also

identify many individuals who do not meet *DSM-IV* diagnostic criteria. These classes generalize across age and sex of the children as well as across different methods of ascertainment and data collection and diagnostic nomenclatures (Neuman et al., 1999). In our larger analysis of female twins, we also identified a relatively uncommon latent class consistent with the *DSM-IV* hyperactive-impulsive subtype of ADHD (Hudziak et al., 1998). This class also contains a number of individuals who did not meet *DSM-IV* diagnostic criteria. In contrast to most clinic-based studies of ADHD, we find that the inattentive ADHD latent class is not associated with an increased frequency of symptoms or diagnoses of disruptive behavior disorders, anxiety disorders, or depression.

Although the presence of these 3 ADHD latent classes is superficially compatible with the categorical definition of *DSM-IV* ADHD, the patterns of symptoms in these classes closely follows patterns of symptoms in other, less severe, latent classes. We have interpreted this to mean that there are 2 or more continua or domains (inattentive, hyperactive-impulsive, or combined) of ADHD problems in the general population and that the latent classes we observe are points along these continua. More recently, however, we have found that the individual latent classes appear to "breed true" in that we do not find the expected increased frequency of twin pairs having a mild and severe form of latent class membership as would be predicted by a continuum model. That is, when both twins have ADHD symptoms, they tend to be in the same latent class. A general model illustrating the difference between such multiple heterogeneity and continuum views is shown in Figure 1.

In summary, our current studies are most compatible with a number of genetically independent forms of ADHD that differ in severity of the symptom domains defined in *DSM-IV* and vary in comorbidity pattern. This suggests that the use of *DSM-IV* diagnostic criteria for genetic studies may be problematic. Perhaps the use of latent class categories or other phenotype definitions will allow the identification of more genetically homogeneous subtypes for study. Furthermore, these results may offer an explanation of why children differentially respond to different treatment paradigms. Different genetic forms of illness might be expected to respond to different interventions.

#### WEB SITES OF INTEREST

<http://www.med.nyu.edu/Psych/addc/addscr.htm>  
<http://www.looksmart.com/eus1/eus317837/eus317920/eus53948/eus84236/eus84243/eus273922/eus280151/?lm&&chl=5&css=1&key=adhd>  
<http://www.sciam.com/1998/0998issue/0998barkley.html>

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