

**“Twin studies and their implications for molecular genetic studies: Are endophenotypes the key to integrating quantitative and molecular genetics in ADHD research?”**

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Quantitative genetic analysis on twin data uses biometric genetic modeling to partition the phenotypic variance within, or the co-variation between, traits into its constituent genetic and environmental influences. One application is to quantify the amount of heritable variance underlying a trait to inform molecular genetic analysis seeking to identify risk alleles associated with the variance in a trait or disorder. The quantitative genetic analysis of Attention Deficit Hyperactivity Disorder (ADHD), either measured as a diagnostic category or as continuous traits through the general population, has turned up consistently high heritability estimates, with average estimates in the region of 60-80% (Burt, 2009; Faraone et al, 2005; Wood et al, submitted). The consistency of the high heritability across ages, populations and definitions of ADHD has lead some researchers to conclude that biometrical genetics has fulfilled its scientific utility in ADHD research and time and money should now be investigated in identifying the functional polymorphisms underlying the disorder. However, candidate gene studies have so far accounted for less than 5% of the estimated heritable variance (DiMaio, et al., 2003; Kuntsi, Neale, Chen, Faraone, & Asherson, 2006). This discrepancy is partly attributable to the problems with defining the ADHD phenotype, centering on low inter rater correlations of about .3 and the heterogeneous nature of the behavioral descriptors of ADHD. Endophenotypes, are stable, heritable measures that are hoped to be a more proximal to the biological etiology of a disorder than the clinical diagnosis itself (Gottesman & Gould, 2003) and thus in part also a truer representation of the underlying genetic liability for a disorder. It is hoped that such measures will aid power in gene hunting studies, however, to date the results have been ‘disappointing’ (Rommelse, 2008). Biometrical genetics offers promise in advancing the search for risk alleles underlying ADHD by revealing the most potentially powerful endophenotypes for molecular genetic analysis, from the many available. Using the examples of mechanical activity level- and reaction time- data this talk will argue that quantitative genetics is still a vital component in a research strategy which leads to molecular genetic analysis in candidate gene- or genome wide association- analysis.