Quantitative Genetics in the Era of Molecular Genetics: Learning Abilities and Disabilities as an Example

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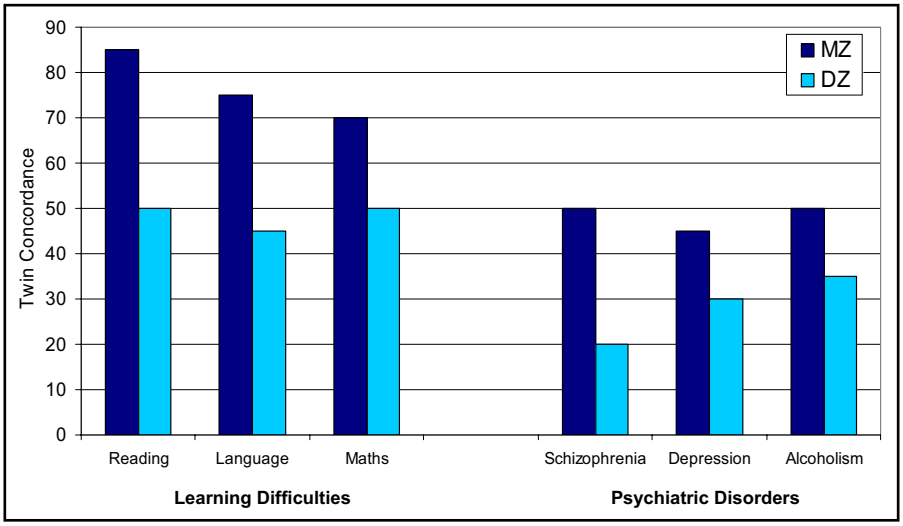
Objective: To consider recent findings from quantitative genetic research in the context of molecular genetic research, especially genome-wide association studies. We focus on findings that go beyond merely estimating heritability. We use learning abilities and disabilities as examples. **Method:** Recent twin research in the area of learning abilities and disabilities was reviewed. **Results:** Three findings from quantitative genetic research stand out for their far-reaching implications for child and adolescent psychiatry. First, common disorders such as learning difficulties are the quantitative extreme of the same genetic factors responsible for genetic influence throughout the normal distribution (the Common Disorders are Quantitative Traits Hypothesis). Second, the same set of genes is largely responsible for genetic influence across diverse learning and cognitive abilities and disabilities (the Generalist Genes Hypothesis). Third, experiences are just as influenced genetically as are behaviors and genetic factors mediate associations between widely used measures of the environment and behavioural outcomes (the Nature of Nurture Hypothesis). **Conclusions:** Quantitative genetics can go far beyond the rudimentary "how much" question about nature versus nurture, and can continue to provide important findings in the era of molecular genetics. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(8):783–793. **Key Words:** quantitative genetics, molecular genetics, twin studies, learning abilities and disabilities

Quantitative genetic research—strain and selection studies in nonhuman animals and twin and adoption studies in our species—has demonstrated the ubiquitous importance of genetic influence on behavioral dimensions and disorders.[1] For learning disabilities, monozygotic (MZ) and dizygotic (DZ) twin concordances are about 85% and 50% respectively for reading; 75% and 45% for language; and 70% and 50% for mathematics.[2] These results indicate substantial genetic influence on learning difficulties, which is greater than for most other common psychiatric disorders. Figure 1 compares results for learning difficulties to those for three psychiatric disorders: schizophrenia (MZ = 50%, DZ = 20%); depression (MZ = 45%, DZ = 30%); and alcoholism (MZ = 50%, DZ = 35%).[1] For the entire range of learning abilities rather than disabilities, heritability estimates are approximately 50%, meaning that approximately half of the variance in learning abilities can be attributed to genetic differences.[3] In terms of public acceptance of these findings, a large survey in the United Kingdom indicated that more than 90% of teachers and parents say that they believe genetics to be at least as important as the environment for learning abilities and disabilities.[4]

Quantitative genetic methods estimate the cumulative effect of genetic influence regardless of the number of genes involved or the magnitude or complexity of their effects. If we could find the genes responsible for heritability, there would be no more need for quantitative genetic designs because genetic influence could be assessed directly from each individual's DNA rather than implied indirectly by genetic relatedness as in twin and adoption studies. However, although genome-wide association (GWA) research has had many successes,[5] it seems highly unlikely

This article is discussed in an editorial by Drs. James J. Hudziak and Stephen V. Faraone on page 729.

FIGURE 1 Monozygotic (MZ) and dizygotic (DZ) twin concordances of learning disabilities and for psychiatric disorders. Note: Data extracted from review by Plomin et al.[1]



that most of the genes responsible for the heritability for any complex trait will be identified in the foreseeable future. The reason is that the largest effect sizes found in GWA efforts to date are very small, which means that many such genes of even smaller effect size will be needed to account for heritability.[6]

The largest effect sizes of replicable associations from GWA studies are odds-ratios of about 1.2 for case-control studies of disorders and less than 1% of the population variance for quantitative traits. These effect sizes are so small that samples in the thousands are needed to identify replicable associations, for example, in case-control studies of schizophrenia,[7] type 2 diabetes,[8] and obesity,[9] and in studies of quantitative traits such as lipids[10] and height.[11] For this reason, it is not surprising that the first GWA study of reading ability that was powered to detect effect sizes of approximately 1% of the variance was unable to detect reliable associations of this magnitude with a sample of 4,000 individuals.[12] Similarly, GWA studies of cognitive abilities were unable to detect reliable associations in studies with 700 subjects[13] and 3,000 subjects.[14] Significant associations with cognition and memory reported in one GWA study with 350 subjects[15,16] have not been replicated.[17]

If the largest effect sizes of replicable associations are so small, hundreds of genes of very small effect size will be needed to account for heritability, which typically is approximately 50%. Moreover, finding the rest of the associations with even smaller effect sizes seems a daunting task; this has been called "the missing heritability" problem.[18] For this reason, molecular genetics seems unlikely to replace quantitative genetics in the foreseeable future. Nonetheless, we hope that our prediction about GWA research is wrong and that it will be possible to identify most of the missing heritability, which, coupled with decreasing genotyping costs, would put quantitative genetics out of business. This hope is not unrealistic in the long term: GWA research began only in 2007 and has searched the genome only for common single-nucleotide polymorphisms (SNPs). Hope for finding the missing heritability springs from the rapid pace of developments in GWA research, which includes other types of polymorphisms such as copy-number variants (CNVs), other rare variants, noncoding RNA, and the entire genome sequence, which will capture variants of any type.[19] Moreover, finding *any* replicable associations between DNA variants and behavior is useful for research purposes as in the case of the *FTO* gene, which is associated with body weight and obesity and is a highly replicated finding across multiple studies.[20]

The GWA finding that many genes of small effect size are responsible for heritability should not have been a surprise, because quantitative genetic research on complex traits in nonhuman animals using the selection design has, for decades, provided evidence that many genes of small effect are involved. If only a few genes