

Genetics of Learning Abilities and Disabilities: Recent Developments from the UK and Possible Directions for Research in China

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Abstract: It is exciting to witness the birth of behavioral genetics in China at a time when the field of genetics is exploding with new discoveries. We begin by discussing the potential for Chinese researchers to sidestep the false starts of previous genetic research on behavior and to become leaders rather than followers in behavioral genetics research. Using learning abilities and disabilities as an example, the rest of the paper considers ways in which quantitative genetic research can go beyond the nature versus nurture question to ask more interesting questions about genetics and psychology. These include the relationship between the normal and abnormal, longitudinal analyses of stability and change, and multivariate analyses of heterogeneity and homogeneity. The most important way to go beyond the rudimentary question about nature versus nurture is to identify the genes responsible for genetic influence on behavior. We briefly describe our quantitative genetic findings and genome-wide association studies of learning ability from the UK Twins Early Development Study (TEDS). It seems a safe prediction that the fast pace of genetic discoveries will continue and will increasingly affect the field of psychology in China and the rest of the world.

Keywords: quantitative behavior genetics; molecular behavior genetics; future development in China

Genetics was one of the major scientific accomplishments of the twentieth century, beginning with the rediscovery of Mendel's laws of heredity and ending with the first draft of the complete DNA sequence of the human genome. The pace of discoveries has continued to accelerate in the first part of the 21st century. One of the most dramatic developments in psychology during the past few decades is the increasing recognition and appreciation of the important contribution of genetic factors. Genetics is central to psychology. Indeed, genetics is central to all the life sciences and gives psychology a place in the biological sciences. Genetics includes diverse research strategies such as twin and adoption studies (called quantitative genetics) that investigate the influence of genetic and environmental factors, as well as strategies to identify specific genes (called molecular genetics). Behavioral genetics is a specialty that applies these genetic research strategies to the study of behavior, such as psychiatric genetics (the genetics of mental illness) and psychopharmacogenetics (the genetics of behavioral responses to drugs).

This special issue of *Acta Psychologica Sinica* comes as the field of behavioral genetics is being born in China, a turning point that offers great potential for advancing the field at a time when research in genetics is exploding with new discoveries and techniques. In this paper, we begin by discussing this potential and then summarize some of our recent behavioral genetic research – both quantitative and molecular genetic research -- on learning abilities and disabilities, with an emphasis on future research directions.

Behavioral Genetics in China

The birth of behavioral genetics in China at this time is especially poignant in the context of the Cultural Revolution. Although the Cultural Revolution was politically motivated, to the extent there was any rationale at all, it was the assumption that all people are the same except for environmental differences. Genetic differences among people were ignored. This environmentalism – we are what we learn – began with the official adoption of Lysenkoism, which explicitly denied the fundamental laws of genetic inheritance discovered by Mendel. Although it is a minor thing compared to the perhaps millions of deaths during the Cultural Revolution, Chinese research in genetics came to a halt.

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But happily China is back as a major contributor in applied genetics in agriculture and animal breeding, in medical genetics, and in basic genetics. This expertise will provide a strong foundation for the growth in the quality and quantity of behavioral genetic research that will occur as centers of excellence are developed in other areas of China in addition to the existing strengths in Beijing and Shanghai, and as genetic expertise in Hong Kong is added to the mix. The great strength of Chinese genetics in animal breeding puts China in an especially strong position for animal model research in behavioral genetics. In addition, because quantitative genetics will continue to play an important role in behavioral genetics even in this age of molecular genetics, the recent creation of Chinese twin registers for children and for adults are important developments.

Although quantitative genetics will continue to be important, the future of behavioral genetic research lies with molecular genetics. Identifying the DNA sequences throughout the genome responsible for the widespread influence of heredity on behavior has ushered in a new era of genetic research on behavior. DNA will integrate behavioral research into the life sciences as we try to understand pathways between genes, brain and behavior. The pace of advances in molecular genetics is amazing. For example, genome-wide association studies have revolutionized gene-finding, using microarrays the size of a postage stamp that can genotype a million DNA markers or assess the RNA expression profile of all of our genes.

As genetic expertise in China is brought to bear on behavior, great advances can be expected in collaboration with the rest of the international scientific community. Because China is coming late to behavioral genetics, Chinese researchers can sidestep the false starts of previous quantitative and molecular genetic research on behavior and become leaders rather than followers in behavioral genetics research. At the most basic level, we hope that Chinese psychologists can skip the fruitless arguments about nature versus nurture and accept that both nature and nurture are important for the development of individual differences in most areas of psychology. A related issue is that quantitative genetic research in psychology should aim to go beyond merely demonstrating genetic influence. As we now know that nearly all behavioral traits show

genetic influence, quantitative genetic studies can move beyond the rudimentary questions about nature and nurture to ask more interesting questions about developmental change and continuity, about genetic homogeneity and heterogeneity, and about the interplay between nature and nurture.

Another example is more mundane but crucial: sample sizes. An important lesson from decades of quantitative genetic research on behavior is that very large sample sizes are needed to yield reliable findings about genetic and environmental parameters. This has been known about quantitative genetic research for decades, especially research that moves beyond the questions about nature versus nurture, as discussed below. During the past decade's molecular genetic research on behavior and other complex traits, the same lesson has been learned: Extremely large samples are needed to detect reliable associations between DNA and complex traits like behavior because hereditary influence is caused by many genes of small effect, a topic to which we shall return. Fortunately, large samples are not a problem in China! For these reasons, it will be exciting to watch the growth of behavioral genetics in China during the next few decades.

Going Beyond Nature versus Nurture: Learning Abilities and Disabilities as an Example of Quantitative Genetic Analyses

In the Twins Early Development Study (TEDS), our quantitative and molecular genetic research focuses on the development of individual differences in learning abilities and disabilities. In this section, we summarize a decade of our quantitative genetic research on this topic in the early school years (Kovas, Haworth, Dale & Plomin, 2007). TEDS began with 15,000 pairs of twins born in the UK in 1994-96 and identified from birth records (Oliver & Plomin, 2007). TEDS twins have been assessed at 2, 3, 4, 7, 9, 10 and 12 years of age, and DNA has been collected from more than 12,000 children. All of the data mentioned in relation to the analyses described in this section are freely available as a zipped SPSS file at the following Web page: <http://www.teds.ac.uk/information/SRCDDataset.htm>.

Despite the importance of learning abilities and disabilities in education and child development, little is known about their genetic and environmental origins in the early school years. Using the TEDS

twin sample, which is representative of the wider UK population, we investigated the genetic and environmental origins of individual differences in performance in academic subjects (English, mathematics, and science) and general cognitive ability (*g*) during the early school years (7, 9 and 10 years of age). As well as estimating genetic influence, the twin method provides estimates for two sources of environmental influence: shared environment and non-shared environment. Shared environmental influences are environments that are common to the twins (e.g. family background), and make members of a twin pair more similar to one another. Non-shared environmental influences are those that are unique to each member of a twin pair (e.g., experiencing an accident or having different peers), that do not contribute to twin similarity.

Because there had been little previous research into the genetic and environmental origins of learning abilities and disabilities in the early school years, we began with the basic nature–nurture question about the relative influence of genes and environment. We were surprised to find that individual differences in early academic performance show substantial genetic influence and modest shared environmental influence. The magnitude of genetic influence was about 65% for year-long teacher assessments of academic performance based on UK National Curriculum criteria and about 55% for direct test data. In the early school years, heritabilities are greater for academic performance (about 60%) than for general cognitive ability (35% on average). We were also surprised to find such consistently high heritabilities of academic performance at 7, 9, and 10 years despite major changes in content across these years. The similarity of results across domains, across ages, and across methods of assessment indicates the robustness of these findings. Results were also similar for boys and girls, as well as for same-sex and opposite-sex DZ twins. These results suggest that quantitative and qualitative sex differences do not play a major role in the origins of individual differences in learning abilities.

It should be emphasized that finding genetic influence will not denigrate the role of education; it will suggest new ways of thinking about effective education, such as recognizing that children create their own experience within the educational process in part on the basis of their genetic propensities. In terms

of public acceptance of such findings, a large UK survey 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 difficulties (Walker & Plomin, 2005). Nonetheless, genetics has scarcely begun to be incorporated into the field of education. For example, textbooks for teachers hardly mention genetics, and few educational journals publish research on the topic. Most importantly, genetics needs to be taken seriously in relation to educational policy because genetic differences contribute at least as much to individual differences in academic performance as do all environmental factors combined.

Research and discussion of the environmental origins of academic performance has focused almost entirely on family background and the school and classroom viewed as shared environmental effects. It is time to change that assumption. Our results indicate that in the early school years there is only a modest role for shared environmental influence (~ 10%) for pairs of children growing up in the same family and being taught in the same school, often by the same teacher in the same classroom. The implication is that most environmental factors that make a difference in the development of learning difficulties are not shared by two children (even MZ twins) growing up in the same family and attending the same schools (Olson, 2007). In fact, even clones (MZ twins) in the same classroom experience different environments (Asbury, Almeida, Hibel, Harlaar & Plomin, submitted).

Little is known about what these so-called ‘non-shared’ environmental factors might be (Plomin, Asbury & Dunn, 2001; Turkheimer & Waldron, 2000), in contrast to the typical ‘shared’ environmental suspects such as family background and school quality that ought to be common to children growing up in the same family. Although non-shared environment can include error, latent variable model-fitting analyses generally exclude error.

A fascinating finding from a recent cross-cultural comparison suggests that heritability is greater and shared environment is lower in countries with a national curriculum as compared to countries where education is decentralized (Samuelsson, Olson, Wadsworth, Corley, DeFries et al., 2007). That is, to the extent that the UK national curriculum imposes equality of educational opportunity, environmental variation between schools is diminished, and thus the

relative contribution of genetic factors to individual differences in academic performance is increased. In contrast, in decentralized educational systems, most notably in the US, variation between schools contributes to environmental variation between children in their academic performance. In this sense, heritability (the magnitude of genetic influence) can be viewed as an index of equality of educational opportunity.

Although these analyses of genetic and environmental influences on individual differences in learning abilities in the early school years yielded some surprising results, the main goal of our program of research was to go beyond these rudimentary issues of nature and nurture in order to address the relationship between the normal and abnormal, longitudinal analyses of stability and change, and multivariate analyses of genetic and environmental heterogeneity and homogeneity between learning abilities.

The Abnormal Is Normal

The previous section considered individual differences throughout the normal distribution, which we refer to as learning abilities. In this section, we focus on the lower end of the distribution, learning disabilities. To what extent are learning disabilities etiologically distinct from the normal range of variation?

Quantitative Trait Locus (QTL) theory posits that genetic influence on common disorders and complex traits is caused by many genes (loci) of small effect rather than by one gene or even by a few genes of large effect (Plomin, Owen, & McGuffin, 1994). Unlike single-gene effects that are necessary and sufficient for the development of a disorder, QTLs contribute interchangeably and additively as probabilistic risk factors. If QTL theory is correct, common disorders such as learning disabilities are likely to be the quantitative extreme of the same genetic factors responsible for variation throughout the distribution. The QTL model refers to quantitative traits even in relation to disorders because if many genes affect a disorder, then it necessarily follows that there will be a quantitative distribution rather than a dichotomy. Stated more provocatively, there is no disability, just low ability -- the abnormal is normal. The ultimate proof of the QTL model will come when QTLs identified for learning disabilities are found to

be associated with the normal range of variation in abilities and vice versa.

Nonetheless, with a large and representative twin sample like TEDS, it is possible to use quantitative genetic techniques (called *liability-threshold model-fitting* and *DeFries-Fulker (DF) extremes analysis*) to compare estimates of genetic and environmental influence for abilities and for disabilities in the same sample. Finding that genetic or environmental estimates differ for abilities and disabilities indicates that there are etiological differences between abilities and disabilities. Using liability-threshold models in TEDS, we found that ACE (A: additive genetic; C: shared (common) environment; E: non-shared environment) results for the lowest 15% of children at each age for all measures are remarkably similar to the individual differences results for the entire distribution. The similarity of ACE results for disability and ability indicates that the quantitative etiologies of disability and ability are similar.

However, differences in the magnitude of genetic and environmental estimates for abilities and disabilities are merely quantitative differences, not qualitative differences. That is, even if heritability differed quantitatively for disabilities and abilities, the same genes could nonetheless be associated with disabilities and abilities. Conversely, heritabilities could be the same for disabilities and abilities and yet different genes could be associated with disabilities and abilities. What we would most like to know is whether there are qualitative differences between disabilities and abilities. That is, are genes associated with learning disability different from the genes associated with normal variation in ability? The DF extremes analysis technique addresses this issue by bringing together dichotomous diagnoses of disability and quantitative traits of ability (see Plomin & Kovas (2005) for an explanation of DF extremes analysis and a discussion of alternative methods). Results from these analyses in TEDS suggest that the etiologies of learning disabilities and abilities are also qualitatively similar.

These results suggest that learning disabilities are the quantitative extreme of the *same* genetic and environmental influences that operate throughout the normal distribution of learning abilities. Using reading disability as an example, when genetic risk factors are identified, we predict that these same genes will be associated with normal variation in

reading ability, not just with reading disability. That is, even in pairs of siblings who are both good readers, we would expect that siblings with one or two copies of a beneficial version of a gene will be better readers than their co-siblings who only have another version of the gene. This conclusion may appear counterintuitive given the long tradition in psychology and education of viewing reading disability as a qualitatively distinct category. However, there is considerable convergence with an emerging cognitive view of variability in reading that emphasizes a continuum of variability.

This finding has profound implications for the diagnosis of learning abilities, because it suggests that we should think about psychological problems in terms of quantitative dimensions rather than qualitative diagnoses. As discussed later, there are many chromosomal and single-gene causes of learning difficulties. However, these are rare and often severe forms of learning difficulties, whereas the quantitative genetic data are telling us that the vast majority of common learning difficulties are the quantitative extreme of the same genetic and environmental factors responsible for normal variation in these learning abilities. Properly understood, these results should help to avoid negative ‘us versus them’ stereotypes about learning difficulties.

Genetic Stability, Environmental Change

To what extent do genetic and environmental influences on learning abilities and disabilities change during development? There are two questions here – a question about quantitative differences in the magnitude of genetic and environmental influences and a question about qualitative changes in genetic and environmental influences. The first question about quantitative differences can be addressed with cross-sectional data, although it is more powerfully addressed when the same children are assessed longitudinally. The second question about qualitative changes from age to age requires longitudinal data.

In TEDS, remarkably similar quantitative ACE estimates (i.e., additive genetic influence, common or shared environment, and nonshared environment, respectively) emerged at 7, 9, and 10 years of age, even for *g* for which the measures were as different as could be at age 7 (telephone testing), 9 (mailed booklet), and 10 (Web-based testing). It is striking

that ACE estimates are so similar across this third of the children’s lives despite major changes in their cognitive development and in the content of the measures. Nonetheless, ACE estimates could be similar from age to age even if different ACE factors operated at each age. Longitudinal analyses of the etiology of age-to-age change and continuity are key to understanding the development of individual differences in learning abilities and disabilities.

The principles of the twin method can be extended to determine the etiology of the covariance between different traits, which is called multivariate genetic analysis. Longitudinal analysis is a special case of multivariate analysis in that it focuses on the etiology of the covariance between the same trait at different ages. In contrast to univariate quantitative genetic analysis that decomposes the variance of a single trait into genetic and environmental sources of variance, multivariate genetic analysis decomposes the covariance between traits into genetic and environmental sources of covariance (Martin & Eaves, 1977).

Genetic Stability. Multivariate genetic analyses yield two types of genetic statistics: bivariate heritability and genetic correlation. *Bivariate heritabilities*, which indicate the proportion of the phenotypic correlation from age to age that is mediated genetically, are about .75 on average for teacher ratings across 7, 9, and 10 years. The reading tests from 7 to 10 years yield a bivariate heritability of .83. These bivariate heritabilities suggest that age-to-age stability of academic and cognitive abilities is largely mediated genetically.

Genetic correlations estimate the extent to which genetic influences at one age correlate with genetic influences at another age regardless of their heritability -- that is, bivariate heritability could be low but genetic correlations could be high. Genetic correlations can be considered as the probability that a gene associated with a trait at one age is also associated with the trait at the other age. The genetic correlations from 7 to 10 years are .67 and .68 for teacher ratings for English and mathematics, respectively, .60 for reading tests, and .72 for *g*. These high genetic correlations across one-third of the children’s lives indicate that genetic effects are largely stable, which is remarkable given the developmental changes during middle childhood. However, because the genetic correlations are not 1.0,

they also suggest some changes in genetic effects from age to age.

Molecular genetic studies that identify the genes responsible for the high heritability of learning abilities and disabilities will provide the definitive test of this conclusion derived from quantitative genetic analyses. These quantitative genetic analyses predict that the chances are about two-thirds that a gene found to be associated with learning abilities at 7 years would also be associated with learning abilities at 10 years. However, this also means that the chances are about one-third that a gene associated at 7 years would not be associated at 10 years.

Environmental Change. Because about 75% of phenotypic stability from 7 to 10 years is mediated genetically, it follows that about 25% is mediated environmentally. Nearly all of this environmental stability is due to shared environment. In terms of environmental correlations rather than bivariate environmental estimates, we found that shared environmental correlations from 7 to 10 years are almost as high as the genetic correlations: .71 for teacher reports of English, .52 for teacher reports of mathematics, and .45 for reading tests, but only .30 for *g*. However, non-shared environmental correlations are uniformly low: .26, .20, .11, and .03, respectively. In other words, non-shared environment largely contributes to change.

What are these non-shared environmental sources of change? Non-shared environment, which accounts for more variance than shared environment, is a major mystery for learning abilities and disabilities because the twins live in the same family, attend the same school, and are often even in the same classroom. Not only do non-shared environmental influences on learning abilities and disabilities not contribute to the similarity of two children in the same family, they also make children at one age different from themselves at another age. The motivation for identifying non-shared environmental features should be at least as strong as the motivation for identifying DNA markers because non-shared environment appears to be the major source of change, and change is the essence of education.

In summary, our longitudinal genetic analyses suggest that age-to-age stability is primarily mediated genetically whereas the environment, especially non-shared environment, contributes to change from age to age.

Generalist Genes, Specialist Environments

A third example of going beyond the basic nature–nurture question is to investigate genetic and environmental links between learning abilities. For example, to what extent do genes that affect reading ability also affect mathematics? Multivariate genetic analysis is well suited to address such questions about genetic heterogeneity and comorbidity.

Generalist Genes. In TEDS, genetic correlations were extraordinarily high within domains: .87 on average for the three components of each domain of teacher ratings. For example, the three domains of English -- reading, writing and speaking -- largely share genetic influence. Similarly high genetic correlations were found within domains for test scores of academic and cognitive performance. This suggests that the components within each domain are nearly the same thing from a genetic perspective. Even more surprising were the high genetic correlations between domains. The average genetic correlation among teacher ratings of English, mathematics, and science at 7, 9, and 10 years was .79. The genetic correlation was .52 between the web-based tests of reading and mathematics at 10 years. Bivariate heritabilities were also substantial: .67 within domains and .64 between domains for ratings for the three ages, which indicates that about two-thirds of the phenotypic correlation between these domains is mediated genetically.

Our results are similar to those of other multivariate genetic studies on learning abilities and disabilities, which consistently yield high genetic correlations. For example, the first study in this area using standard measures of reading and mathematics reported a genetic correlation of .98 between reading and mathematics (Thompson, Detterman, & Plomin, 1991). In a recent review, genetic correlations varied from .67 to 1.0 for reading versus language (five studies), from .47 to .98 for reading versus mathematics (three studies), and from .59 to .98 for language versus mathematics (two studies) (Plomin & Kovas, 2005). The average genetic correlation between domains was about .70. We refer to these genetic effects as ‘generalist genes’ in order to highlight the general effect of genes within and between learning abilities and disabilities (Plomin & Kovas, 2005).

We also found that some of these generalist genes that affect learning abilities are even more general in that they also affect other sorts of cognitive

abilities included in the general cognitive ability (g) factor. In TEDS, the average genetic correlation between learning abilities and g is about .60. But academic performance is not just g . Although about a third of the genetic variance of English and mathematics is in common with g , about a third of the genetic variance is general to academic performance but not g .

Similar to issues discussed above in relation to genetic stability, the fact that genetic correlations are not 1.0 means that there are also genes that contribute to predisposing children to perform better in one domain than another. Because genetic influence on learning abilities is substantial, such specialist genes contribute importantly to dissociations among learning abilities even though most genes are generalists.

Again, definitive proof of the importance of generalist genes will come from molecular genetic research. The prediction is clear: Most (but not all) genes found to be associated with a particular learning ability or disability (such as reading) will also be associated with other learning abilities and disabilities (such as mathematics). In addition, most (but not all) of these generalist genes for learning abilities (such as reading and mathematics) will also be associated with other cognitive abilities (such as memory and spatial).

When these generalist genes are identified, they will greatly accelerate research on general mechanisms at all levels of analysis from genes to brain to behavior. Implications of generalist genes for cognitive and brain sciences and for education have recently been discussed (Kovas & Plomin, 2006; Plomin, Kovas & Haworth, 2007). The most immediate implication is that, from a genetic perspective, learning disabilities are not distinct diagnostic entities. Even before finding the genes, putting together these two quantitative genetic findings – that children with learning difficulties differ quantitatively not qualitatively and that genetic effects are general – implies that genetic nosology differs from current diagnoses based on symptoms. First, the genetic data suggest that there are no disabilities: Common learning disabilities are only the low end of the normal bell-shaped distribution of abilities. Second, because genetic effects are general, they blur distinctions between ostensibly different problems such as difficulties with reading and with mathematics. That is, most of what is going on

genetically has broad general effects rather than specific effects on just one difficulty. However, these implications will remain at a conceptual level until genes are found that are responsible for these genetic effects. When these genes are found, their implications for prediction and intervention may be even greater than their effect on diagnosis.

Much remains to be learned from classical twin studies of learning difficulties and abilities, and this is a highly active area of research (Olson, 2007). For example, one new direction is research on development, such as the transition from pre-reading skills in early childhood to learning to read in the early school years (Byrne, Samuelsson, Wadsworth, Hulslander, Corley et al., 2007; Petrill, Deater-Deckard, Thompson, Schatschneider, DeThorne et al., 2007). Another developmental example is the transition in middle childhood from learning to read to reading to learn (Harlaar, Dale & Plomin, 2007; Keenan, Betjemann, Wadsworth, DeFries & Olson, 2006). An area of research with huge potential that has only begun to be explored in relation to learning abilities and difficulties is the developmental interplay between genes and environment (Plomin, DeFries, McClearn & McGuffin, 2008).

Specialist environments. Multivariate genetic research also has an interesting story to tell about environmental influences on learning abilities and disabilities. Shared environmental influences are also generalists: Shared environmental correlations are at least as high as genetic correlations. However, non-shared environmental correlations are on average half the magnitude of the genetic correlations, about .40 on average within and between learning abilities, although they vary considerably across domains. Non-shared environmental correlations between learning abilities and g are very low, about .10 on average.

We conclude that non-shared environmental influence is largely specific to each learning ability. This adds another piece to the puzzle of non-shared environment. As noted in the previous section, not only do non-shared environmental influences on learning abilities make two children in the same family different from one another, but they also make children at one age different from themselves at another age. Now we add the additional clue that these non-shared environmental influences also make children different across domains of learning. In other words, non-shared environments are specialists. One

implication of this conclusion is that educational influences might have their greatest impact on remediating discrepant performances among learning abilities such as differences in children's performance in reading and mathematics.

Molecular Genetic Analysis

Quantitative genetic analyses will continue to make fundamental contributions to understanding the etiology of individual differences in behavior; in fact, they will be increasingly in demand because they can chart the course for molecular genetic research. For example, our quantitative genetic analyses described above indicate that learning abilities and disabilities are highly heritable even in the early school years, which suggests that learning abilities and disabilities in the early school years are good targets for molecular genetic research. The finding of genetic stability recommends the use of measures across time rather than relying on a single measurement occasion. The 'generalist genes' finding suggests that molecular genetic studies would profit from multivariate approaches that focus on comorbidity rather than heterogeneity because the genetic action lies in what different abilities and disabilities have in common. Although it is usually assumed that phenotypic specificity is better for gene-hunting, cognitive abilities are interesting because multivariate quantitative genetic evidence consistently points in the opposite direction. It is an important issue because the generalist genes hypothesis suggests that attempts to focus on *specific* learning disabilities – for example, reading disability independent of any other learning disabilities – will capture less of the genetic action because most genetic effects on learning disabilities are general.

The most far-reaching implications for molecular genetics come from the finding that the same genes affect disabilities and abilities (see 'the abnormal is normal' section above). This finding suggests the need for a QTL perspective: Learning disabilities are the quantitative extremes of the same genetic and environmental factors responsible for the normal distributions of learning abilities (Plomin & Kovas, 2005). The QTL perspective suggests switching from case-control designs to quantitative traits because we are losing information by making a discrete variable out of something that is inherently continuous. It also raises the specter that genetic influences on complex

traits and common disorders are due to many genes of small effect size, which will require very large samples and powerful techniques to detect them. The slow progress towards identifying genes responsible for heritability of common disorders and complex traits is in part due to the lack of power to detect small QTL effects.

During the past few years, genome-wide association studies with large samples have revolutionized gene-hunting research (Wellcome Trust Case Control Consortium, 2007). Genome-wide studies, which capture variation across the whole genome rather than focusing on specific candidate genes, have been made possible by microarrays ('gene chips') that can genotype a million DNA markers simultaneously (Plomin & Schalkwyk, 2007). Because microarrays are relatively expensive and can be used only once, the costs of such a study are prohibitive for the large samples needed to detect small QTL effects. For this reason, we have developed a technique called SNPMap (SNP Microarrays and Pooling) in which small amounts of DNA from many individuals are pooled in a single test tube and the pooled DNA is genotyped on a single microarray (Butcher, Meaburn, Liu, Hill, Al-Chalabi et al., 2004). Using DNA from a TEDS sample of about 8000 children (4000 twin pairs), we have conducted the first genome-wide QTL association studies on reading ability (Meaburn, Harlaar, Craig, Schalkwyk & Plomin, 2008) and on *g* (Butcher, Davis, Craig & Plomin, 2007). Following the QTL perspective, we pooled DNA for individuals low versus high on a quantitative trait score for reading or *g* to screen for the largest allele frequency differences between the low and high groups. We then tested nominated QTLs by individually genotyping them in a large independent unselected sample. Using our two-stage design, we identified 10 SNPs associated with reading and 6 SNPs associated with *g*. Although we had 95% power to detect associations that account for 0.5% of the variance of these quantitative traits, the largest association accounted for only 0.4% of the variance and the average effect size was only 0.2%.

These associations await additional replication in other studies, which is crucial because non-replication is rife, in part because many previous studies have been greatly underpowered to detect and to replicate QTL associations of such small effect size. Sequential

replication designs with very large sample sizes will be needed rather than a single study because of the problem of multiple testing when using hundreds of thousands of DNA markers in genome-wide association studies. Another implication of small effect sizes is that perhaps hundreds of reliably associated DNA markers will be needed to reach useful levels of prediction of genetic risk. Although the task of identifying genes for common disorders and complex traits in psychology is more difficult than had been anticipated, the quantitative genetic evidence for substantial heritability is strong and variation in DNA sequence is responsible for this heritability. The pace of discovery in molecular genetics warrants optimism for progress. For example, two new developments are already making their mark: the importance of non-coding DNA that is transcribed into RNA but not translated into amino acid sequences -- which redefines what the word *gene* means -- and the discovery of greater than expected structural variation in DNA sequence such as deletions and duplications (called *copy number variation*) (Plomin & Davis, in press). The ultimate goal of molecular genetic studies is to sequence each individual's entire genome, which has begun to happen.

The only safe prediction is that the fast pace of genetic discoveries will continue and will increasingly affect research in psychology in China and the rest of the world. Reliable associations can be compiled on a DNA microarray which will make it possible to use hundreds of genes to predict genetic risk and to use these sets of genes in top-down behavioral genomic research that explores developmental change and continuity, multivariate heterogeneity and comorbidity, and gene-environment interaction and correlation (Harlaar, Butcher, Meaburn, Craig & Plomin, 2005). A crucial question is whether the prediction of genetic risk will be sufficiently robust to translate into genetically based diagnoses, personalized treatments, and prevention programs.

Although identifying sets of genes associated with learning difficulties is unlikely to have much direct impact on teachers in the classroom confronted with a particular child with a learning difficulty, the capability of predicting genetic risk from DNA will have far-reaching implications in terms of diagnosis, treatment and intervention (Plomin & Walker, 2003). As indicated earlier, gene-based diagnoses of learning

difficulties are likely to be very different from current diagnoses. For example, many of the same genes (the 'generalist genes' mentioned earlier) that predict reading difficulty will also predict mathematics difficulty, although some genes will be specific. That is, a learning disabilities gene chip in the future would mostly contain genes that can predict which children are likely to have general problems with reading *and* mathematics, but it would also contain some genes that can predict specific problems with reading *or* mathematics. Moreover, genes on the learning difficulties gene chip that predict learning difficulties will also predict normal variation in learning abilities, as well as high ability, which means that these genes will be useful for predicting the educational progress of all children, not just children at the low end of the normal distribution. Identifying these genes will lead to dimensional rather than diagnostic systems of classification of learning abilities and disabilities, based on etiology rather than symptomatology. It will also lead to research on the brain and mind pathways between genes and behaviour that can account for these general as well as specific effects (Kovas & Plomin, 2006).

A learning difficulties gene chip could be even more important for treatment and intervention than for diagnosis. In terms of treatment, an untapped opportunity for genetic research is to identify genes that predict, not disorders themselves, but response to treatment. This goal is part of a 'personalized treatment' movement rather than imposing one-size-fits-all treatments. However, the most important benefit of identifying genes associated with learning difficulties is the power to predict problems very early in life, which will not only serve as the earliest possible warning system but also facilitate research on interventions that prevent learning difficulties from developing, rather than waiting until problems are so severe that they can no longer be ignored. This goal is achievable even in the case of skills such as reading that do not occur until later in development. Reading is a good example because there is a large and widely accepted body of evidence that phonology -- and specifically the ability to reflect on the sound structure of spoken words -- lies at the core of reading development and reading problems. The goal of early intervention fits with a general trend toward preventative medicine which is much more cost-effective for children as well as for society. Because

vulnerability to learning difficulties involves many genes of small effect size, genetic engineering is unimaginable for learning difficulties; interventions will rely on environmental engineering, not genetic engineering.

It could be argued that genetics is unimportant because we need to provide resources to prevent children from falling off the low end of the bell curve, regardless of the causes of their poor performance. However, genetics is likely to facilitate the development of successful preventative interventions that can focus on diagnoses based on etiology rather than symptomatology. Genetics can also help to target children most likely to profit from interventions. Targeting is likely to be important because successful prevention programs usually require extensive and intensive, and thus expensive, interventions.

What about the ethical issues raised by finding genes associated with learning abilities and difficulties? For example, will gene chips justify social inequality? Knowledge alone does not account for societal and political decisions. Values are just as important in the decision-making process. Decisions both good and bad can be made with or without knowledge. Finding genetic influence on reading ability does not mean that we ought to put all our resources into educating the best readers and forgetting the rest. Depending on our values, genetics could be used to argue for devoting more resources to help disadvantaged children. Indeed, genetics makes this view more palatable because it avoids assigning blame for poor reading solely to environmental failures of the school and family.

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学习能力与学习障碍的遗传学： 英国的近期发展和中国的研究的可能方向

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摘要：中国的行为遗传学诞生在遗传学突飞猛进的时代，令人振奋。作为一个新兴学科，中国的行为遗传学研究可以避免走前人的弯路，而成为领先而不是滞后的领域。以学习能力的研究为例，计量行为遗传学可以避免“性与养”（nature vs. nurture）的争论而直接研究一些遗传学与心理学里有意义的问题，包括正常与异常、稳定与变动、同质与异质的关系等问题。尤为重要是超越“性与养”的争论而直接研究遗传对行为的影响。本文也扼要介绍了英国“双生子早期发展”项目的计量行为遗传学和“全基因组关联”对学习能力的研究结果。可以预计，飞速发展的遗传学发现将会持续一些时日，其发展将会对中国和世界的心理学产生更大的影响。

关键词：计量行为遗传学；分子行为遗传学；中国今后的学科发展

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