Genes, Environment, and Dyslexia
The 2005 Norman Geschwind Memorial Lecture

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This article presents an overview of some methods and results from our continuing studies of genetic and environmental influences on dyslexia, and on individual differences across the normal range that have been conducted over the past 25 years in the Colorado Learning Disabilities Research Center (CLDRC) and in related projects. CLDRC investigators compare the similarities of identical twin pairs who share all their genes and fraternal twins who share half their segregating genes to assess the balance of genetic, shared family environment, and nonshared environment influences on dyslexia and on individual differences across the normal range. We have learned that among the children we have studied in Colorado, group deficits in reading (dyslexia) and individual differences in reading across the normal range are primarily due to genetic influences, and these genetic influences are often shared with some of the same genetic influences on deficits and individual differences in language and ADHD. We have also learned from our molecular-genetic linkage studies that there are regions on several chromosomes likely to contain genes that influence dyslexia. Several specific genes within these regions have been tentatively identified through molecular-genetic association analyses, but much more research is needed to understand the pathways among specific genes, regions of noncoding DNA that regulate the activity of those genes, the brain, and dyslexia. I conclude with a discussion of our research on individual differences in early reading development, on the role of early learning constraints in dyslexia, and on how genetic influences are expressed through their interaction and correlation with the environment.

Key Words: Behavioral genetics, development, dyslexia, environment, genes, reading disability, twins

INTRODUCTION

I was most grateful and honored to be invited by the IDA to give the Norman Geschwind Memorial Lecture. Dr. Geschwind was a giant in the field of language disorders and he recognized the important role

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that genetic influences may play in their etiology. When I first met Dr. Geschwind in the early 1980s and proclaimed my excitement about our new behavior genetic studies of dyslexia, his response was something like ". . . well, genes of course, but how do they influence the brain?" Later in the paper, I will give an update of what I think we have learned over the past years in answer to that question.

For more than 25 years, I have enjoyed the combination of basic science and applied interests of the IDA membership and the many IDA conference presentations that I have attended on the problem of dyslexia and its related disorders. I have also enjoyed presenting occasional lectures to much smaller groups at previous IDA conferences. When I contemplated speaking to a much larger audience of IDA members for the Geschwind Memorial Lecture, I decided to depart somewhat from my usual focus on the details of specific studies and present a broader historical perspective on the work we have been doing in the Colorado Learning Disabilities Research Center and in our earlier Colorado Reading Project over the past 27 years. That is also the general goal of this paper.

In outline, my specific goals in the paper are to: 1) begin with a brief historical overview of the CLDRC and the Colorado Reading Project while introducing my wonderful coinvestigators and some of the main themes of our research; 2) describe the CLDRC twin sample, how we define dyslexia, and some of the behavior-genetic methods that allow us to estimate the average influences of genes, shared family environment, and nonshared environment on dyslexia; 3) present some recent results from our behavior genetic analyses from the different projects; 4) discuss the results of our recent molecular genetic analyses with a cautionary note about their interpretation and application; and 5) conclude with some results from our International Longitudinal Twin Study of individual differences in prereading and early reading development.

SECTION I: HISTORY OF THE CLDRC

Our "Center" status began in 1990 when the National Institutes of Child Health and Human Development (NICHD) began funding four different research centers for the study of learning disabilities. Prior to our designation as a Center, we had been funded since 1979 by NICHD as a Program Project that we called the "Colorado Reading Project." This project, directed by John DeFries at the University of Colorado Institute for Behavioral Genetics, was initially focused from 1979 to 1982 on the development and validation of measures for reading and related skills. Beginning in 1983, these measures were administered in our behavior genetic studies of identical and fraternal twin pairs with at least one member having a school history of reading disability, and in control twin pairs with no school history of reading problems. Our sample of twins has been growing since that time, with new measures and methods of analysis being introduced across the

different funding cycles. For example, John DeFries and David Fulker (1985, 1988) developed a powerful method for estimating the genetic contribution to group deficits in normally distributed skills, including reading. This has come to be known as the DF method. Their application of the DF method with a small early twin sample from the Colorado Reading Project yielded the first direct evidence for significant genetic influence on the group-deficit in reading in a school-based sample (DeFries, Fulker, & LaBuda, 1987). Another important development during this period was the addition of Drs. Shelley Smith (University of Nebraska) and Bruce Pennington (University of Denver) as coinvestigators to include their pioneering molecular-genetic research to identify areas of chromosomes containing a gene or genes related to dyslexia (Smith, Kimberling, Pennington, & Lubs, 1983). A third major addition to our research on dyslexia in the late 1980s was supported by separate grants from NICHD to study the use of talking computers for the remediation of dyslexia in collaboration with Barbara Wise.

When the CLDRC was initially funded under the direction of John DeFries in 1990, a new project directed by Bruce Pennington began ascertaining and testing twin pairs that included at least one member with Attention Deficit Hyperactivity Disorder (ADHD). Although many people do not think of ADHD as a learning disability, it often co-occurs with reading disability (Pennington, 2006). We wanted to discover the genetic and environmental etiology of this comorbidity, and also understand the relations among executive function skills assessed in Bruce's laboratory, ADHD, and the reading skills assessed in the other CLDRC projects.

During the second Center funding cycle from 1996 to 2000, we added a project to provide additional support for our computer-based remediation research, and CLDRC investigators began collaborating with Brian Byrne from the University of New England, Australia, on a twin study of individual differences in prereading and early reading development. While this on-going International Longitudinal Twin Study is not specifically focused on dyslexia and is funded separately from the current CLDRC, its results have important implications for the genetic and environmental etiology of early reading disabilities that I will discuss in the final section of the paper.

A major addition to the CLDRC in 2000 included a stronger focus on reading and language comprehension in a new project directed by Jan Keenan (my lovely wife) at the University of Denver. The CLDRC had previously focused primarily on deficits in printed word recognition and related skills, reflecting the commonly held view that deficits in printed word decoding were the primary cause of failures in the ultimate goal of reading, the comprehension of extended text. An example of this view is contained in the definition of dyslexia adopted by the IDA Board on November 12, 2002, which emphasized that deficits in reading comprehension were "secondary consequences" of deficits in printed word decoding. However, other research had shown that

reading comprehension failures could occur that were at least partly independent from problems with word recognition, particularly when children moved from "learning to read" in the early grades to "reading to learn" in the later grades (for review, see Leach, Scarborough, & Rescorla, 2003). Therefore, we introduced several new assessments for reading comprehension, listening comprehension, and other related skills that are being administered in Jan's laboratory at the University of Denver. Although the twin sample for these new measures is still of limited size, preliminary analyses have shown a significant genetic correlation for individual differences in word recognition and reading comprehension, but also significant *independent* genetic influences on reading comprehension that are associated with genetic influences on listening comprehension. Taken together, genetic influences on word recognition and listening comprehension account for all of the genetic influences on reading comprehension (Keenan, Betjemann, Wadsworth, DeFries, & Olson, 2006), indicating a largely genetic basis for the "simple model" of individual differences in reading comprehension proposed by Hoover and Gough (1990).

The present CLDRC projects and coinvestigators included in our recently funded five-year renewal are outlined below.

I. Twin studies (psychometric assessment) (John DeFries, Sally Wadsworth, Erik Willcutt)
II. Reading and language processes (Jan Keenan, Richard Olson)
III. ADHD and executive function (Bruce Pennington, Erik Willcutt)
IV. DNA linkage analysis and physical mapping (Shelley Smith, Michael Salbaum)
V. Response to computer-assisted instruction for reading difficulties (Barbara Wise, Brian Byrne, Ron Cole, Sarel van Vuuren)

The next main section of the paper describes the twins and nontwin siblings who participate in Projects I–III, and outlines the logic of our behavior genetic analyses of dyslexia

SECTION II: BEHAVIOR GENETIC ANALYSIS OF DYSLEXIA IN THE CLDRC

OUR TWIN SAMPLES AND HOW WE DEFINE DYSLEXIA

Individual differences in reading ability are normally distributed in the population (c.f., Shaywitz et al., 1992). The large Isle of Wight study by Yule, Rutter, Berger, and Thompson (1974) seemed to suggest that the distribution was "skewed," and contained more poor readers in the low tail than would be expected in a normal distribution that has equal numbers of people in the high and low tails. However, analyses conducted by Rodgers (1983) demonstrated that deviations from the normal distribution in the Isle of Wight study were probably caused by problems in sensitivity of the tests to individual differences at higher levels of reading ability.

The normal distribution is more popularly known as the "bell curve." Its shape reflects the fact that for any complex human behavior such as reading, many different positive and negative influences will combine in different ways to produce different skill levels across individuals, with most people having a mix of influences that places them near the middle of the bell curve, where the greater height of the curve means more people in that range of ability. Fewer people will be so unfortunate or fortunate to have a mix of influences that are more extremely negative or extremely positive that would place them in the low-ability or high-ability tails of the distribution. This has two important consequences for diagnosis and research in dyslexia.

The problematic consequence for the diagnosis of dyslexia is that in spite of the frequent and varying citations in the literature about the percentage of children who have dyslexia, dyslexia does not exist as a discrete diagnostic category that is distinctly separate from the normal population distribution. Statements about the percent of children or adults with dyslexia are based on arbitrary cut points on the low-ability tail of the normal distribution, and this is true even if some sort of IQ-reading-discrepancy criterion is employed. Thus, dyslexia exists on a continuum of severity from the lowest readers to those with milder cases. Again, where we draw the line is arbitrary. It will certainly influence the range of severity within the diagnostic category, and more severe selections may increase the ratio of males to females (Olson, 2002) and possibly the specific genes that are involved (Deffenbacher et al., 2004), but changing the severity criterion does not significantly change average estimates of genetic and environmental influences on dyslexia (Hawke, Wadsworth, Olson, & DeFries, in press). I will have more to say about this later.

The positive consequence of the bell-curve in reading research is that it allows us to apply powerful statistical methods in our genetic analyses of dyslexia and individual differences that depend on normal distributions for the skills that we study. I will show why this is so after commenting on how we recruit our twin sample in the CLDRC.

We have worked with 27 different school districts along the Colorado Front Range within about 150 miles of Denver. The schools' administrative staff identify twins in the third through 12th grades by their same last name and birthdays, and then send letters to their parents to get permission for us to examine their twins' school records for a broadly defined school history of reading problems and/or ADHD. Pairs where one or both twins have this school history, siblings of these twins, and control twins with no school history are then invited to be tested in our Boulder and Denver laboratories.

To be identified as members of a low reading skill group to assess the average genetic and environmental influences on reading disability, we require that the twins have a positive school history for reading disability and that they meet a severity criterion that varies somewhat in different studies, but is usually about 1.5 standard deviations below our normal control-twin average, roughly the lower 5 to

10 percent of readers in our Colorado sample. We typically also include a minimum IQ criterion of 85 or 90 on the Wechsler (1991) verbal or performance subscales, but some analyses include the full range of IQ down to the lowest scores of about 60 in our sample to see how that influences the heritability estimates. Other criteria include no uncorrected sensory deficits and no seizures.

Perhaps the most significant exclusionary criterion in our Colorado sample is that we do not include twins who are learning to read English as a second language, an obviously influential environmental contribution to reading failure for many children in Colorado. It is always important to consider the effects of the environmental range on behavior genetic estimates of genetic and environmental influences. In populations where the range of environmental supports and constraints on reading development is very large, environmental factors will be the primary influence. In contrast, when we study genetic and environmental influences in populations with universal and relatively uniform environmental support for reading development, and exclude obvious environmental factors such as learning to read in a second language, genes may play the dominant role for both dyslexia and individual differences across the normal range, as you will see that they do, on average, for the twins in our Colorado samples.

THE BASIC LOGIC OF THE TWIN METHOD FOR ESTIMATING GENETIC AND ENVIRONMENTAL INFLUENCES

Our behavior-genetic analyses depend on a wonderful natural experiment, the existence of monozygotic (MZ) identical twins who share all their genes, and dizygotic (DZ) fraternal twins who share half their segregating genes on average. If genetic factors are important for dyslexia, we would expect that MZ twins would be more likely than DZ twins to share the disorder. If genes were the only cause of dyslexia, MZ twins would always share dyslexia, and approximately half of the DZ twins would also share dyslexia, because they share half of their segregating genes on average. However, this extreme genetic pattern is not what we have found in our Colorado twin sample, and this means that there are significant environmental influences as well.

These environmental influences can be divided into two types. One is due to shared family environment factors such as family reading habits or school quality that tend to make twins similar regardless of their genetic similarity. (The twins in our study are all reared in the same homes and nearly all share their schools as well.) If dyslexia were entirely due to shared family environment, then twins growing up in the same family would always share the disorder regardless of their genetic similarity, but again, this is not what we have found. The other type of environmental influence estimated in our behavior genetic analyses is from nonshared environment influences that make twins in both MZ and DZ pairs different from each other such as birth accidents or disease, and any measurement errors that are not shared by the twins. The average influence from these nonshared environment factors that make

twins different can be estimated simply by observing the average difference between MZ twins, since they share all their genes and their family environment. If nonshared environment were the only influence on dyslexia, then twins in a pair, regardless of their genetic similarity and their shared family environment, would be no more likely to share dyslexia than two unrelated people picked at random from the population. Again, that is not what we have found. What we have found are patterns of average MZ and DZ twin similarities that fall between these three extreme examples, indicating a mixture of genetic, shared environment, and nonshared environment influences that may differ in their importance, depending on the specific reading and related skills that we have measured, and other factors I will mention later.

Our estimates of the specific proportions for genetic influences and the two types of environmental influences on low-group membership (in contrast to individual differences across the full normal distribution considered in the final section) for reading and related skills are based on the powerful DF regression method developed by DeFries and Fulker (1985, 1988). This analysis takes advantage of the normal distribution of reading ability in the population. First, we identify twins as reading disabled if they fall below our severity criterion for a measure of interest, and we compute their average scores separately for MZ and DZ twins. The twins in this deficit group are called "probands." The other members of the MZ and DZ pairs are called the "cotwins," who may also be probands if they fall below the severity criterion. The basic idea behind DF regression analyses is that the difference in average regression toward the population mean for MZ versus DZ cotwins can be used to estimate the proportions of influence on the probands' group deficit from genes and from shared environment, while also taking into account the nonshared environment influences that are directly indicated by the average MZ cotwin regression toward the population mean.

SECTION III: SOME RESULTS FROM OUR DF ANALYSES OF DYSLEXIA

DF analyses of dyslexia in the CLDRC have addressed several different types of questions. I will begin this section with results from DF analyses of group deficits in several specific reading and related skills. Then I will consider how subtypes or dimensions of individual differences are related to the strength of genetic influences on dyslexia. Finally I will present results from DF analyses that allow us to estimate the extent of *shared* genetic influences on group deficits in different reading skills, language skills, and Attention Deficit Hyperactivity Disorder (ADHD).

UNIVARIATE DF RESULTS FOR INDIVIDUAL SKILLS

The MZ and DZ proband and cotwin group means for a composite measure of printed word recognition are presented in Figure 1, based

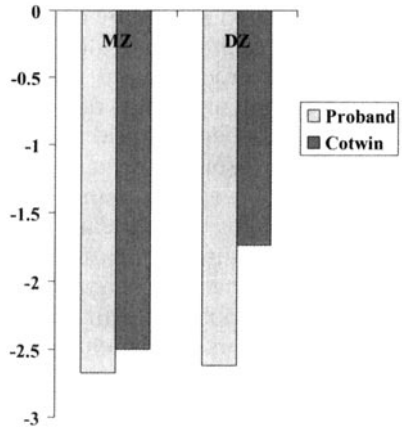

Figure 1. MZ and DZ proband and cotwin group means for word recognition deficits in standard deviation units below the normal population mean.

on results from Gayán and Olson (2001). The MZ and DZ proband group means fall similarly far below the normal control twin mean in standard deviation units, but their respective cotwin group means show a very different pattern of regression toward the population mean. Note that there is only a small amount of regression for the MZ cotwin group, suggesting a small proportion of nonshared environment influences (including measurement error) on the group deficit. In contrast, the average regression for the DZ cotwin group mean is much greater, suggesting significant genetic influences. If genes were the only influence on low group membership, the DZ cotwin group mean would be expected to regress about half way to the population mean because DZ twins share half of their segregating genes on average. The fact that the DZ cotwin group mean regressed less than half way to the population mean, but more than 50% of that distance, suggests that over 50% of the group deficit in printed word recognition is due to genetic influences.

Figure 2 presents the proportion estimates for genetic (54%), shared environment (40%), and nonshared environment (6%) influences, based on DF analysis of the individual twin data that contributed to the means shown in Figure 1 for the group deficit in word recognition. It is important to understand that these percentages and others I will mention throughout this article are called "estimates" because we want to infer what the percentages are for the whole population based on our limited samples. The estimates are precise within our samples, but the samples are small enough that they leave some uncertainty due to possible sampling error about what the actual values are for the whole population. Fortunately, there are statistical methods for estimating what we call "confidence intervals" for the population values, given our sample size and the individual data. These confidence intervals allow us to say, for example, that for our

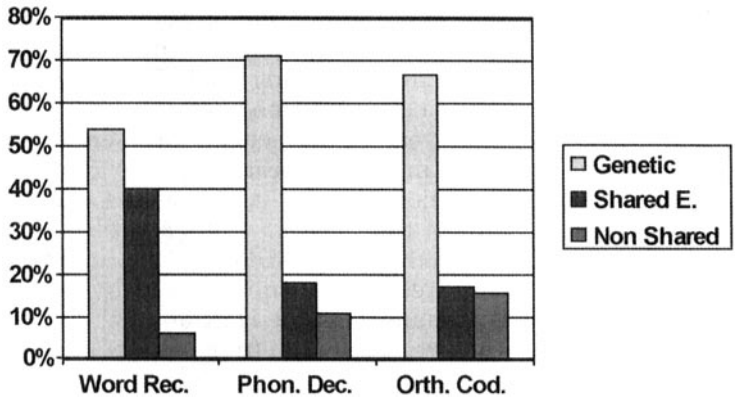

Figure 2. Estimates of the percentages for genetic, shared environment (Shared E.), and nonshared environment (Non Shared) influences on group deficits in word recognition (Word Rec), phonological decoding (Phon. Dec.), and orthographic coding (Orth. Cod.).

estimate of 54% genetic influence on the group deficit in word recognition from a sample of 215 MZ and 159 DZ twins in this analysis (Gayán & Olson, 2001), the most likely population estimate is 54%, and there is a 95% probability (a commonly used confidence level) that the actual percentage in the population is between 40% and 70%. I will not continue to provide confidence intervals for genetic and environmental estimates in this article. These details can be found in the cited studies.

Gayán and Olson (2001) also used the DF method with their measures of component skills in word reading as shown in Figure 2 for phonological decoding (oral nonword reading), and orthographic coding (choosing the word from word-pseudohomophone pairs such as rane rain). The group deficit in phonological decoding was strongly influenced by genes (71%), and much less so by shared environment (18%). A similar pattern was observed for the group deficit in orthographic coding wherein 67% of the deficit was due to genes and 17% was due to shared environment influences. (An earlier study by Olson et al., 1989, reported no significant genetic influence on orthographic coding, but this was due to its small sample size.) Gayán and Olson also observed strong genetic influences (72%) and weak shared environment influences (14%) on the group deficit in a language measure of phoneme awareness.

Many of the DF analyses conducted by John DeFries and coinvestigators in Center Project I have used a composite reading score based on combining the Peabody Individual Achievement Tests of word reading, spelling, and reading comprehension (Dunn & Markwardt, 1970). In a recent DF analysis with this composite score, genes accounted for 58% of the group deficit (Wadsworth & DeFries, 2005).

A recent independent study by Harlaar, Spinath, Dale, & Plomin (2005) used the DF model to estimate genetic and environmental influences on the group reading deficit for first grade (mean age 7 years) twins in England who were below the 10th percentile on the TOWRE test of word and nonword reading efficiency (Torgesen, Wagner, & Rashotte, 1999). The twins in the low reading group were selected from a much larger population sample that included a total of 3,909 twin pairs with data from the TOWRE. This sample was much younger (mean age 7 years) than our CLDRC sample (mean age 11.5 years), and the TOWRE test was administered by telephone. Nevertheless, the overall results from the Harlaar et. al. DF analyses were quite similar to what we have found from our laboratory testing of older Colorado twins in the CLDRC.

ARE THERE "SUBTYPE" DIFFERENCES IN GENETIC INFLUENCES ON DYSLEXIA?

When we estimate genetic and environmental influences on group deficits, these are *average* estimates for the group. They do not indicate, for example, that 54% of individual probands have deficits in word recognition that are due only to genes, as one might mistakenly infer from Figure 2. Rather, the mix of genetic and environmental influences most certainly varies continuously across individuals. To better understand the varying contributions from genes and environment in different individuals with dyslexia, we have used a modification of the DF method to see if the average influence of genes on reading and related deficits varies significantly ($p < .05$, or less than a 5% probability that the difference is due to chance), depending on individual proband characteristics such as gender, severity, age, IQ, and phonological versus surface dyslexia.

Keep in mind that this method tests the significance of differences in the magnitude of genetic influences relative to environmental influences across subtypes or dimensions of individual differences, but it does not specify the mechanisms of genetic influence. Thus, it is possible that even though the magnitudes of genetic influence are not different across subtypes, there still could be subtype differences in the specific genes that are involved. Furthermore, even if the magnitudes of genetic influence do differ across subtypes, it is possible that the same genes are involved, but the relative magnitude of environmental influences differs between subtypes (see Geschwind's hypothesis for gender differences in the next section).

Gender. Wadsworth and DeFries (2005) found that the magnitudes of genetic influences for males (53%) and for females (63%) on the group deficit in a composite reading measure were not significantly different in our CLDRC sample. A smaller study by Stevenson (1992) with twins from the London area came to the same conclusion. In contrast, results from the recent study by Harlaar et al. (2005) with younger English twins found an opposite pattern; genetic influences accounted for 68% of the group deficit in males and 50% of the group

deficit in females when probands were selected below the 10th percentile. Although this difference was not statistically significant, a more severe selection below the fifth percentile did result in significantly more genetic influence on the group deficit for males (72%) than for females (37%).

Wadsworth and DeFries (2005) wondered if these results were due to the much younger sample in the Harlaar et al. (2005) study (mean age 7 years) compared to the CLDRC sample (mean age 11.5 years). Therefore, Wadsworth and DeFries split their sample at the mean age of 11.5 years and compared results for the younger half (mean age 9.6 years) and the older half (mean age 14.1 years). The younger half of the sample showed the same nonsignificant pattern of stronger genetic influence for females (67%) than for males (53%), although Wadsworth and DeFries acknowledged that their younger group still was older than the twins in the Harlaar et al. study. In the future, we will be able to assess gender differences in genetic influence at age 7 in our International Longitudinal Twin Study to see if we can replicate the Harlaar et al. result. If we find that even our 7-year-old female twins also tend to show slightly stronger genetic influence and less environmental influence for their group deficit, this would be consistent with Norman Geschwind's (1981) interesting hypothesis that girls might be less susceptible to environmental influences such as teaching methods, differences in socioeconomic status, or societal pressures.

Severity and Age. We have not found significant differences in the magnitude of genetic influences on dyslexia that are related to severity of selection (Hawke, Wadsworth, Olson, & DeFries, in press), though in the next section on our molecular genetic research, I will discuss possible differences in the specific genes that are involved at different levels of severity. We have also found no significant differences in the magnitude of genetic influences on reading and spelling disabilities related to age within the 8 to 18 year age range of the CLDRC sample (Friend, DeFries, Wadsworth, & Olson, in press). However, there are other subtypes or dimensions of individual differences that have been linked to significant differences in the genetic etiology of dyslexia.

IQ. Olson, Datta, Gayán, and DeFries (1999) found that deficits in printed word recognition were significantly more heritable for children with dyslexia who were higher on a continuous IQ dimension. Similarly, Wadsworth, Olson, Pennington, and DeFries (2000) found significantly greater genetic influences on a composite measure of word recognition, spelling, and reading comprehension in children above 100 IQ (72% genetic) compared to children below 100 IQ (43% genetic). We agree with Lyon et al. (2001) that these results should not be taken as a justification for excluding children with lower IQ scores from remedial services since environmental factors may play an even stronger role within this group.

Olson el al. (1999) noted that the lower IQ groups' greater environmental influence was largely due to shared family environment.

We speculated that the shared family environmental range might be greater for reading development among children with lower IQ scores. We noted that parents' years of education were significantly lower for probands' with lower IQ scores, and this could be related to greater variation in the home and school support for reading among children with lower IQ scores. In recent unpublished analyses, we have begun to explore the relations between the magnitudes of genetic influences on group deficits in different reading skills and parents' average years of education. Genetic influences are significantly weaker and shared environmental influences are stronger on the probands' group deficit when parents have less education. Further research is needed to confirm our hypothesis that differences in environmental range are responsible for the differences we have found in genetic estimates related to IQ and parent education. An alternative hypothesis is that children in the low IQ or parent education subgroups are more sensitive to variation in the environment.

Phonological and Surface Dyslexia. Castles, Datta, Gayán, and Olson (1999) compared the magnitudes of genetic and environmental influences on "surface dyslexia" (relatively poor reading of unusual exception words compared to nonwords) and "phonological dyslexia" (relatively good reading of unusual exception words compared to nonwords). Genetic influences on deficits in a composite measure of word reading were significantly greater for children who fit the profile of "phonological dyslexia." We hypothesized that relatively good reading of unusual exception words compared to nonwords reflected reading failure in spite of the higher level of print exposure needed to learn how to read the exception words. In contrast, when nonword reading is relatively better than exception word reading, this may indicate poor reading due to less print exposure rather than to genetic constraints on phonological decoding and word recognition.

BIVARIATE DF ANALYSES OF SHARED GENETIC INFLUENCES ACROSS DIFFERENT SKILL DEFICITS

In addition to estimating the magnitude of genetic influences on the group deficit for a specific measure, we can also use the DF method to estimate genetic influences on the correlation between deficits in two different variables. This is accomplished by selecting probands on one variable and observing cotwin regression to the mean on a second variable. If there is some shared genetic influence for group deficits on the two variables, DZ cotwins will show greater regression than MZ cotwins toward the population mean for the second variable. Moreover, when the estimate of bivariate heritability is adjusted by the univariate heritabilities for the two variables, we can obtain an estimate of the genetic correlation, which is a measure of the extent to which the two variables are influenced by the same genes (Knopik, Alarcon, & DeFries, 1997).

The bivariate DF method was used by Gayán and Olson (2001) to estimate genetic correlations between group deficits in several differ-

ent skills including word recognition, phonological decoding, orthographic coding, and phoneme awareness. They found on one extreme that the genetic correlation between group deficits in word recognition and phonological decoding (oral nonword reading) was .99, so virtually the same genes are playing a role in those group deficits. On the other extreme, the genetic correlation between phoneme awareness (phoneme deletion) and orthographic coding was only .28, and significantly lower than the genetic correlation of .67 between phoneme awareness and phonological decoding. These results provide important information on the genetic overlap and genetic independence for deficits in different reading-related skills, and they provide guidance for the interpretation of results from molecular genetic studies of different skills that I will consider in the next section.

We have also used the bivariate DF method to assess the shared genetic influence on dyslexia and ADHD (Willcutt et al., 2003). About 30% of our Colorado probands with dyslexia also have ADHD, and bivariate DF analyses have shown that there is a significant shared genetic etiology between dyslexia and the attention deficit component of ADHD, but not with the hyperactivity component.

SECTION IV: MOLECULAR GENETIC LINKAGE AND ASSOCIATION STUDIES

LINKAGE ANALYSIS

The CLDRC Project IV directed by Shelley Smith has used two complementary methods to discover genes related to dyslexia. The first method, called "linkage analysis," uses DNA markers to identify areas within the 23 pairs of chromosomes that may include a gene or genes involved in dyslexia. Due to the process called "crossing over" in the production of parents' sperm and egg cells during meiosis, nonidentical twins and ordinary siblings may share the same identical segment of DNA on both corresponding regions of a chromosome pair, on just one member of a pair, or on neither member of a pair. If siblings with higher genetic similarity at a given chromosomal region are significantly more likely to share dyslexia, then there is evidence that dyslexia is "linked" to a gene or genes in that region.

It is important to keep in mind that statistically significant evidence for linkage of dyslexia to a particular region of the genome does not necessarily mean that a gene in that region is responsible for all or even most cases of genetically influenced dyslexia. Although linkage analyses are capable of locating regions including major gene effects for a disorder, the results from many different linkage analyses for dyslexia suggest that there are a number of different chromosomal regions and related genes that may be involved, each of these genes may account for only a small proportion of the genetic influence on dyslexia in the population, and the specific genes responsible may vary across different individuals (Fisher & DeFries, 2002; Pennington & Olson, 2005; Smith, Kimberling, & Pennington, 1991).

ASSOCIATION ANALYSIS

The most replicated linkage region for dyslexia, first discovered by CLDRC investigators on the short arm of chromosome 6 by Cardon et al. (1994), has been intensively studied in several different laboratories through a second molecular genetic method called "association" analysis. This method compares dyslexic and control group frequencies of DNA base-pair sequences that differ between individuals at specific locations in the genome. When the frequency of a base-pair sequence is significantly different between groups with and without dyslexia, the sequence that is more common in the group with dyslexia, called the risk allele, is said to be associated with the presence of dyslexia. The associated risk allele could be contained within a coding region of a gene that directly influences the nature of the protein produced through that gene, or in a nearby noncoding region that can moderate the amount of protein produced through that gene.

Combined linkage and association analyses of CLDRC sibling pairs in Shelley Smith's laboratory by Deffenbacher et al. (2004) and in Jeff Gruen's laboratory by Kaplan et al. (2002) identified a small region on the short arm of chromosome 6 containing several different genes that may be related to dyslexia. This group of genes has been identified in subsequent association analyses of a combined CLDRC and U.K. sample by Francks et al. (2004), and in an independent U.K. sample by Cope et al. (2005). Two genes in this area have attracted particular interest and more detailed DNA sequence analyses. Meng, Smith et al. (2005) in Jeff Gruen's laboratory identified markers in a noncoding region of the DCDC2 gene that were significantly associated with dyslexia in our CLDRC twin and sibling sample. This same gene was also associated with dyslexia (specifically severe spelling disability) in a German sample (Schumacher et al., 2006). Studies in the U.K. by Cope et al. and more recently by Paracchini et al. (2006) have focused their attention on the nearby KIAA0319 gene that also has shown significant association with dyslexia.

"WELL, GENES OF COURSE, BUT HOW DO THEY INFLUENCE THE BRAIN?"

The excellent Norman Geschwind Memorial Lecture given by Albert Galaburda (2005) addressed the above question that Geschwind posed to me in the early 1980s. Galaburda cited a recent association study that reported a variant of the EKN1 gene on chromosome 15 was related to dyslexia in a group of Finish families (Taipale et al., 2003). Galaburda then presented evidence that mutations in the EKN1 gene could result in abnormal neuronal migration and disrupted auditory processing in rats, and he suggested that this might also cause dyslexia in humans. The Taipale et al. association result has not been replicated in other samples including one from the CLDRC (Meng, Hager et al., 2005), but Galaburda's hypothesis of abnormal neuronal migration has also been suggested as an explanation for effects of the risk alleles re-

lated to the DCDC2 and KIAA0319 genes on chromosome 6 (Meng, Smith et al., 2005; Paracchini et al., 2006; Shumacher et al., 2006). Meng, Smith et al. showed that "knocking out" the DCDC2 gene in mice resulted in grossly abnormal neuronal migration during brain development. Paracchini et al. (2006) observed a similar disruption of neuronal migration when they interfered with the expression of the KIAA0319 gene in rats. In addition, Paracchini et al. noted that in human lymphoblastoid cell lines that were heterozygous for the KIAA0319 risk allele, the protein level generated from the chromosomes carrying the risk allele was relatively lower (about 40%) compared to the level of protein from chromosomes carrying nonrisk alleles.

These remarkable results may seem to support the diagnosis of dyslexia through DNA analysis for the DCDC2 and/or KIAA0319 risk alleles, but unfortunately, the relations between these risk alleles and dyslexia are both complicated and tenuous. Paracchini et al. noted that the risk allele for KIAA0319 ". . . had an increased frequency of up to 28% only in the most severe dyslexic cases, whereas it showed the same frequency of 16% in the complete set of dyslexic probands as in a control population." They added that, "It is likely that the reduced expression of KIAA0319 is not sufficient by itself to cause RD [dyslexia] but that this has an impact on reading abilities only when combined with other genetic or environmental factors" (p. 1664). Deffenbacher et al. (2004) and Schumacher et al. (2006) also noted that their positive linkage and association results depended on a severe selection criterion.

Thus, it is clear that while there are very promising developments in research on how the DCDC2 and KIAA0319 genes may influence brain development and dyslexia, much further research is needed to replicate these results and to directly observe the effects of these risk alleles on human brain development and behavior, possibly in interaction with other risk alleles and environmental factors. In addition, it is clear that the risk alleles identified on chromosome 6 account for only a small proportion of children and adults with dyslexia. There most certainly are other genes yet to be discovered, particularly for less severe cases of dyslexia.

In response to the Meng, Smith et al. (2005) results that were reported at the 2005 meeting of the American Society for Human Genetics, a science writer for the *New York Times* made the following statement (Blakeslee, 2005): "Researchers said that a genetic test for dyslexia should be available within a year or less. Children in families that have a history of the disorder could then be tested, with a cheek swab, before they are exposed to reading instruction. If children carry a genetic risk, they could be placed in early intervention programs." A few months after the *Times* article was published and after I had presented my Geschwind Memorial Lecture, I learned that many parents were calling the IDA office to find out how they could get this genetic "dyslexia test" for their children (G. Eden, personal communication, February 23, 2006). Guinevere asked me if I could offer a clarifying

statement about the implications of recent association studies for such a test.

Here is my statement.

> Better prediction of children's risk for dyslexia, prior to formal reading instruction in the schools, is an important long-term goal of our molecular genetic research. However, I believe that much more research will be needed before we can use cheek swabs and DNA analyses to significantly improve prediction of dyslexia beyond what we can glean from family history and prereading assessments of reading related skills. First, the results from recent molecular genetic association studies need to be replicated in other laboratories and with other independent samples. Second, the risk alleles identified to date are also present in many children who do not have dyslexia, so their effects may depend on complex interactions or additive influences from other genes and/or the environment. More research is needed to discover those genes and environmental risk factors before these risk alleles will be very useful for the prediction of dyslexia. Third, it appears that the specific alleles identified to date may account for only a modest proportion of the most severe cases of dyslexia and very few, if any, of the less severe cases. We have learned from our behavior genetic studies with twins that genetic influences are equally strong for less severe dyslexia, so there are likely to be other risk alleles that have yet to be discovered. These risk alleles are likely to be numerous and of small average effect in the population with dyslexia, since whole-genome linkage scans for dyslexia have often yielded inconsistent results. In conclusion, the evidence to date suggests a complex pattern of genetic influence on dyslexia that may involve many different genes of small effect, and the specific genes may vary across individuals. In view of its apparent complex genetic etiology, I do not believe we are close to having a useful DNA test of genetic risk for dyslexia at this time. But I also believe that this goal is one we should continue to vigorously pursue, along with the rapid advances in methods for efficiently mapping the human genome. I am sure there will be substantial benefits for many children when we can use DNA analyses to improve the early prediction of genetic risk for dyslexia, and to achieve a better understanding of the interactions between genes, the developing brain, and reading.

Results from behavior genetic studies with twins can compliment molecular genetic research on dyslexia by identifying the most heritable reading and related skills, the most heritable subtypes of dyslexia, and the kinds of environmental influences that may add to or interact with genetic influences. Behavior genetic studies can also help with the interpretation of results from linkage and association studies that include multiple measures of reading and related skills, as we will see in answer to the following question.

ARE THERE DIFFERENT GENES FOR DEFICITS IN DIFFERENT READING SKILLS?

This is a very interesting question. A number of linkage and association studies, including those conducted with the CLDRC twin and sib-

ling sample, have reported significant linkage and association results for deficits on some reading measures, but not others at specific loci in the genome. Schumacher et al. (2006) found significant association for their DCDC2 risk allele with spelling disabilities, but not with disabilities in word and nonword reading accuracy in their German sample. Meng, Smith et al. (2005) reported significant DCDC2 association for deficits in a composite measure of word reading, spelling, and reading comprehension, but some other reading measures such as word recognition were not significantly associated. Similar variability in the significance of association for different but highly correlated reading measures has been noted in other association analyses conducted with the CLDRC sample (Deffenbacher et al., 2004; Francks et al., 2004; Kaplan et al., 2002). However, the fact that some measures reach a statistical boundary for significance while others fail to reach that significance criterion does not mean that the level of linkage and/or association is significantly different *between* the measures. The studies conducted to date do not have the much larger sample sizes that would be needed to detect significant differences in linkage and association *between* different reading skills. Therefore, the authors of the above studies with the CLDRC sample have made no claims for such differences.

However, other studies have suggested that there are different genes for deficits in different reading skills (c.f., Grigorenko et al., 1997; Grigorenko, Wood, Meyer, & Pauls, 2000). Most recently, Igo et al. (2006) reported from a combined linkage and segregation analysis that a new locus on chromosome 13 is linked to group deficits in a word reading efficiency (fluency) measure, but not to group deficits in word reading accuracy, which instead was significantly linked to regions on chromosomes 12 and 15. They argued that their results supported distinctly different genetic mechanisms for deficits in word reading efficiency (fluency) and word reading accuracy. However, I do not believe that there is sufficient statistical power in this study, or in any of the other studies conducted to date, that is needed to detect significant *differences* in linkage or association for different reading and related skills. One skill might cross a threshold of statistical significance for linkage or association at a given locus while another might not, but that does not imply that the difference in linkage or association is statistically significant.

Of course, a lack of statistical power to detect differences in reading skill-specific gene effects from linkage and association studies does not preclude their existence. The evidence I mentioned earlier from behavior genetic analyses of genetic correlations between group deficits in different measures can help guide our search for skill-specific genes. The nearly perfect genetic correlations between deficits in some skills such as word and nonword reading reported by Gayán and Olson (2001, 2003) suggest that any differences in their linkage and association results would most likely be due to chance. Other skills such as word recognition and listening comprehension make

partly independent genetic contributions to reading comprehension (Keenan et al., 2006), so we might expect to find at least some differences in the specific genes contributing to individual differences in these skills. Another example is the partly independent genetic influences we have found for the phonological decoding and orthographic coding component skills in word recognition (Gayán & Olson, 2001, 2003). On the other hand, the genetic correlations between the skills in these two examples, though significantly less than perfect, were substantial at about .8. This means that we are likely to find many genes that contribute to deficits and individual differences in both skills, genes that Plomin and Kovas (2005) have referred to as "generalist genes." Recent advances in multivariate linkage analyses for correlated reading and related skills may speed the discovery of these "generalist genes" (Marlow et al., 2003).

ARE THE SAME GENES INVOLVED IN DYSLEXIA AND ADHD?

Behavior-genetic evidence reviewed by Willcutt et al. (2003) suggested that the answer is yes, at least in some cases, particularly for the attention deficit component of ADHD. Moreover, Gayán et al. (2005) recently reported results from the fist bivariate linkage scan showing that the co-occurrence of dyslexia and ADHD in the CLDRC sample is significantly linked to the most replicated region for dyslexia on chromosome 6 as well as to regions on chromosomes 14, 13, and 20. Further research will determine if these new linkage areas can be replicated, and if there are additional regions of the genome that may contribute to the combination of dyslexia and ADHD. There may also be regions that are linked to these disorders independently. This novel bivariate linkage analysis illustrates the broad range of questions about the genetic etiology of dyslexia and related disorders that are being addressed in the CLDRC through complementary behavior genetic studies with twins and molecular genetic studies of DNA.

DF ANALYSES OF HIGH READING ABILITY

To conclude this section on DF analyses of dyslexia and provide a transition to the next section on individual differences across the normal range, it is interesting to note that DF analyses for group deficits in reading can also be applied to assess the genetic and environmental etiology of high reading ability. Boada et al. (2002) performed this analysis with the CLDRC twin sample that had no school history of reading difficulty in either member of the pair. When proband members of the twin pairs were selected for *high* performance at least one standard deviation above the population mean on the same PIAT composite score used by Wadsworth and DeFries (2005) for their low-group DF analyses of dyslexia, average DZ cotwin regression down toward the population mean was significantly greater than for MZ cotwins. Moreover, the resulting estimate of genetic influence on high-group membership (54%) was very similar to Wadsworth and DeFries' estimate for low group membership (58%). This result leads

naturally to the question of genetic and environmental influences on individual differences across the whole normal distribution. Are those influences similar in magnitude to influences on the low and high tails of the distribution?

SECTION V: GENETIC AND ENVIRONMENTAL INFLUENCES ON INDIVIDUAL DIFFERENCES

My goals in this section of the paper are first, to consider the genetic etiology of dyslexia in the context of individual differences across the normal range; second, to discuss the idea that the genetic influences on dyslexia and individual differences in reading ability are at least partly through their direct influence on learning rates for reading and related skills; and third, to conclude with a discussion of how genes influence reading ability through their interaction and correlation with the environment, including environmental interventions for dyslexia.

DYSLEXIA AND INDIVIDUAL DIFFERENCES ACROSS THE NORMAL RANGE

A different kind of analysis is used to estimate genetic and environmental influences on individual differences in the whole population, including the low and high tails of the normal distribution. This analysis is based essentially on comparing the correlations for MZ and DZ twins across a representative population sample, wherein, for example, complete genetic influence would be indicated by a perfect correlation of 1 for MZ twins, and a correlation of .5 for DZ twins who share half their segregating genes, on average. Harlaar et al. (2005) applied a related method of analysis to estimate genetic and environmental influences on individual differences in TOWRE word and nonword reading efficiency at the end of first grade in their large and representative population sample of MZ and DZ twins born in England and Wales from 1994 through 1996. Their estimate of genetic influences (65%) on individual differences in boys' combined word and nonword reading efficiency in the whole population sample was very close to their estimate of genetic influences on boys' group membership below the 10th percentile (67%) that I mentioned in Section III. Harlaar et al. and Plomin and Kovas (2005) have argued that the similar estimates indicate that the same genes influence low-group membership and individual differences across the normal range. Pennington and Olson (2005) allowed that this may be true for many genes, but we noted that the DCDC2 and KIAA0319 genes I discussed in Section IV seemed to be influencing only the most severe cases of dyslexia.

To better understand the development of genetic and environmental influences on individual differences in reading ability, our International (Australia, Colorado, and Scandinavia) Longitudinal Twin Study (ILTS) begins its assessments at preschool age 4–5 years,

with follow up assessments at the end of kindergarten, first grade, and second grade (Byrne et al., 2006, in press; Samuelsson et al., 2005, in press). We are examining a broad range of reading and related skills at each test occasion. I will focus first on the results for a measure of preschool print knowledge, and then on results for the combined TOWRE word and nonword reading efficiency measure at the end of kindergarten and first grade.

Individual differences in preschool print knowledge, including letter names and sounds (most children could not read any words) were mostly due to variations in shared family environment (68%), though genetic influence (23%) was also statistically significant. These estimates are from a combined sample of Australian, U.S., and Scandinavian twins (Byrne et al., 2006), and they are similar to the estimates within each country (Samuelsson et al., in press). In contrast, when children begin to receive formal reading instruction in school, genes become the dominant influence on individual differences in reading and spelling.

Formal reading instruction in school occurs with differing intensity and consistency at different times, depending on country. There is a lot of direct reading instruction in the Australian full-day kindergarten classes from the Sydney area, where individual differences in TOWRE word and nonword reading efficiency are strongly influenced by genes, and shared environment influences are not statistically significant by the end of kindergarten (Byrne et al., in press). In Colorado, there is more limited and varied formal reading instruction among the half-day kindergarten classes, and both genetic (62%) and shared environment influences (30%) are significant for TOWRE performance at the end of kindergarten. In Scandinavia, there is practically no reading instruction in kindergarten classes or in the twins' homes, and shared environment influences (51%) are stronger than genetic influences (38%) by the end of kindergarten (from unpublished analyses presented by Samuelsson et al., 2006). Formal reading instruction is first introduced in Scandinavian schools during the first grade. By the end of first grade, genetic influences account for more than 75% of individual differences in Scandinavia, as they do at the end of first grade in the Australian and Colorado samples. The shift in the Colorado sample from primarily shared environment influence on preschool print knowledge to increasing genetic influence on TOWRE reading through the end of kindergarten and first grade is shown in Figure 3.

I previously hypothesized that the increase in genetic estimates from those influencing preschool print knowledge to those influencing reading after a year of formal reading instruction is due to the greater environmental range for print exposure and home or preschool class instruction among preschool children. Another hypothesis is that our twins' performance on our measures of print knowledge in preschool depended less on the complex cognitive skills involved in learning to read, whose individual differences may be

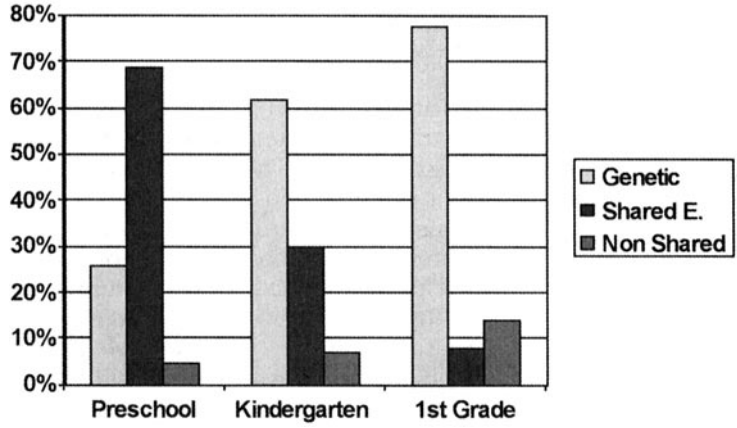

Figure 3. Estimates of the percentages for genetic, shared environment (Shared E.), and nonshared environment (Non Shared) for individual differences in preschool print knowledge, end of kindergarten TOWRE reading, and end of first grade TOWRE reading, for the Colorado twin cohort.

more strongly influenced by genes. A test of this hypothesis would be to introduce formal reading instruction for preschool twins and assess genetic influences on their response to that instruction. I don't recommend doing this study because I believe it increases the risk of reading failure for some children with delayed language development, but my prediction is that genetic influences on response to formal preschool reading instruction would be just as strong as on responses to reading instruction in our Australian sample by the end of kindergarten, and in the U.S. and Scandinavian samples by the end of first grade.

In summary, the pattern of results across three countries shows that genes are the main influence on individual differences in response to early reading instruction in the schools, as they are for twins in England at the end of first grade (Harlaar et al., 2005). A similar result has been reported by Petrill et al. (in press) from an independent study of first and second grade twins in Ohio. On the Woodcock (1989) reading comprehension measure that is common to both the Petrill et al. and ILTS studies, the Petrill et al. estimate of genetic influences on individual differences (76%) was very similar to the estimates for this measure from the ILTS samples (77%) at the end of first grade.

HOW DO GENES INFLUENCE INDIVIDUAL DIFFERENCES IN READING, AND DYSLEXIA?

Through Phonological Awareness? We assess a number of nonreading cognitive and perceptual skills in our twin studies to address the above question, including phonological awareness. Individual differences in phonological awareness among the ILTS twins were significantly influenced by genes beginning in preschool (61%), and its

genetic correlation with the genes that influence preschool print knowledge (68%) was also significant (Samuelsson et al., 2005; Byrne et al., 2006). Byrne et al. (2006) performed a longitudinal analysis to assess the shared genetic influence between preschool phonological awareness and TOWRE reading at the end of kindergarten for the combined U.S. and Australian samples. The shared genetic influence for preschool phonological awareness and kindergarten reading was statistically significant, but not after controlling for the genetic influences that phonological awareness shared with preschool print knowledge. In contrast, preschool print knowledge had significant shared genetic influences with kindergarten reading, even after controlling for genetic influences it shared with preschool phonological awareness. Therefore, preschool phonological awareness is only part of the genetic pathway to later reading. Other genetic influences on how quickly children learn about print prior to kindergarten are independently influencing individual differences in subsequent reading growth rates. One of these partly independent genetic influences may be related to individual differences and deficits in processing speed on tasks such as rapid automatic naming (RAN), particularly among children with severe dyslexia (Compton et al., 2001), and among children with both dyslexia and ADHD (Shanahan et al., in press).

Through Direct Genetic Influences on Learning Rates for Reading and Related Skills? Direct genetic influences on individual differences in learning *rates* for reading and related skills, including phonological awareness, may be the major source of genetic influences on both dyslexia and individual differences in reading ability across the normal range. The previous sentence may seem to be a tautology, but what I mean by "direct" is that the primary genetic influence is on how quickly children learn with a given amount of instruction and reading practice. One can imagine a more indirect genetic influence on learning rates for prereading and early reading skills that could come from genetic influences on temperament and activity level that lead to differences in reading motivation and reading practice. Reading motivation and reading practice are positively correlated with reading ability (Wigfield & Guthrie, 1997), but this simple correlation does not specify the causal direction. It could be primarily from motivation and practice to reading ability, or it could be primarily from reading ability to motivation and practice (Morgan et al., in press). Consistent with the direct learning-rate view of the causal direction, Stanovich (1986, p. 364) has argued that early failures in learning due to deficits in cognitive skills such as phonological awareness are the primary cause of the correlation, and consistent reading failure leads to a ". . . causal chain of escalating negative side effects." These secondary effects may include less motivation to read and less reading practice.

One way to address this question is to examine children's response to instruction in a controlled experimental setting. Byrne, Fielding-Barnsley, and Ashley (2000) found that children who participated in a highly structured preschool training program for phoneme

awareness varied widely in their subsequent reading development through the early grades. The best preschool predictor of their later reading development was the number of training sessions that were needed for them to reach a criterion level for phoneme awareness.

Some readers of this article may be struck by the relation between the Byrne et al. (2000) study and the current emphasis on the early assessment of children's Response to Instruction (RTI) in the schools for the diagnosis and treatment of reading disabilities (c.f., Vaughn & Fuchs, 2003). The most recent call for learning disability research center proposals from the NICHD strongly supported the use of RTI in the diagnosis and treatment of reading disabilities. I will discuss how the CLDRC has responded to this call in the next concluding section of the paper on the complex relations between genetic and environmental influences on reading ability.

GENES AND THE ENVIRONMENT

Teacher and School Effects. The evidence for very strong average genetic influences on individual differences in reading ability and for dyslexia by the end of first grade does not diminish the importance of the environment for reading development. Obviously, we would not be reading at all without the cultural invention of writing systems and formal education in the use of those systems. Strong genetic influence on individual differences in reading does not deny the importance of formal instruction for children learning to read, but it does suggest that variation in the quality and quantity of that instruction within our twin samples has *relatively* little influence on individual differences in reading at the end of first grade, compared to the approximately 75% influence from genes.

This result seems inconsistent with the predominant view associated with the No Child Left Behind legislation that emphasizes school and teacher quality as the primary causal factors for students' reading failure. We do not have direct measures of teacher quality, but we have compared the correlations for twins that share the same teachers and twins that have different teachers in first grade. If differences in teacher quality have a strong average influence on individual differences in the twins' reading ability, twin correlations for reading ability at the end of first grade should be significantly higher for those twin pairs who share the same teacher than for those who have different teachers. However, there is no significant difference between these correlations in the ILTS Colorado twin cohort tested at the end of first grade. For example, the TOWRE composite word and nonword reading efficiency measure's correlation for 60 pairs of MZ twins sharing the same first grade teacher (.90) is only slightly and nonsignificantly higher than the correlation for 74 pairs of MZ twins with different teachers (.83). Moreover, among the much larger sample of U.K. twins tested by telephone with the TOWRE near the end of first grade by Harlaar et al. (2005), the correlation for 1038 MZ pairs with the same first grade teacher (.86) was very close to the correlation for 578 MZ

pairs with different teachers (.85) (N. Harlaar, personal communication, September 10, 2006).

The lack of evidence for significant teacher effects on individual differences in twin studies is consistent with the results from regression analyses by Mehta, Foorman, Branum-Martin, and Taylor (2005). They found that teacher effects on student performance from the beginning to the end of a grade are not significant for reading skills after controlling for initial student performance, though there was evidence for small but statistically significant teacher effects on writing.

Although the average effects of differences in teacher quality on individual differences in reading appear to be quite limited, these effects could be substantial among a small minority of extremely ineffective or extremely effective teachers. Moats and Foorman (2003) have suggested that broad improvements in teachers' education for instructing and motivating students to read would have a positive influence on students' reading achievement, particularly for the lower readers. I agree that improved teacher training could have this desirable result, though genetic and broad cultural constraints may still keep some children from reaching and maintaining the "grade-level" goal of No Child Left Behind, and genes could still be the dominant influence on individual differences and low performance within this higher range of reading ability.

What about school effects? The schools attended by the Colorado ILTS twin cohort vary significantly in their third-grade students' average reading performance on the Colorado Student Assessment Program (CSAP) reading and writing test that is given in compliance with the No Child Left Behind legislation. Nearly all the twins within the sample pairs attend the same school, so we cannot compare twin correlations for those pairs attending the same or different schools in the way that we compared correlations for twins with the same or different teachers. However, we can look at the strength of the correlation between the twins' performance on our reading measures at the end of second grade and their school's average student performance on the third grade CSAP test. Those correlations were low but statistically significant, ranging from .12 to .14 across four different reading and spelling measures (Olson et al., 2006). These correlations may seem surprisingly low given the significant variation in average student CSAP performance across the many different schools attended by our twins. However, the variation in average school CSAP scores is far less than the variation in individual CSAP scores within schools, which may be largely due to genes.

Parents' years of education was significantly correlated at .4 with the average CSAP score in their twins' schools, so it is possible that our significant school CSAP correlations with the twins' reading are due to family characteristics rather than quality or quantity of reading instruction in the school. Therefore, we also looked at the correlations between average school performance on the CSAP and the twins' reading skills after controlling for parents' average years of education

(Olson et al., 2006). With this statistical control, the correlations between the twins' reading scores and their schools' average CSAP scores approached 0 and were not statistically significant. A similar result has been reported by McCoach, O'Connell, Reis, and Levitt (2006) for nontwin samples of kindergarten and first grade students, wherein school differences in average reading performance were generally small and often not significant after controlling for student and family characteristics at the beginning of school.

The nonsignificant correlations after controlling for parent education and other measures of SES in the Olson et al. (2006) and McCoach et al. (2006) studies do not prove that differences in school instruction have no influence on differences in student performance. It is quite possible that the quality and quantity of reading instruction tends to be somewhat lower in schools that have lower average levels of parent education. In this case, statistically controlling for parent education or other measures of SES could mask a small (first order correlations of .12 to .14) but direct influence on students' reading growth from differences in schools' reading instruction. Moreover, there is strong experimental evidence for significant school effects from studies of district-wide reading reform, including a recent study in Colorado. A large increase in the quantity and quality of reading instruction in a previously low performing Colorado school district improved students' average third grade CSAP reading performance significantly, raising it above the state average (Sadoski and Wilson, 2006). Thus, although genes are the dominant influence on individual differences across the normal ecology of schools in our sampling areas, it is clear that significant improvements in instruction and reading practice can result in significant average gains for students' reading skills in the early grades, even though genes would probably continue to be the primary influence on individual differences across this higher range of reading ability.

Gene-environment Correlations and Interactions. Genetic influences on dyslexia and individual differences across the normal range may often be mediated by what we refer to as gene-environment correlations and interactions (Moffitt, Caspi, & Rutter, 2005; Turkheimer et al., 2003). In this section of the paper, I will focus on one very important gene-environment correlation: the relation between low reading skill and subnormal levels of reading practice.

I previously discussed evidence that preschool children's learning rate for phoneme awareness in a structured training program is a strong predictor of later reading ability (Byrne et al., 2000), and I argued that direct genetic influences on slow learning rates for phoneme awareness and grapheme/phoneme correspondences may be an important causal influence on dyslexia (see also Snowling & Hayiou-Thomas, 2006). These genetic influences on dyslexia through slow learning rates for reading and related skills may often be amplified by children's early frustration and failure in learning to read that results in their withdrawal from reading practice (Stanovich, 1986). Thus,

their genetically influenced learning difficulties lead them to select an environment of very little reading. This type of genotype-environment correlation may be exactly the opposite of what these children need. They need *more* than normal levels of reading practice to eventually reach, or more closely approach, a normal level of reading skill.

Wise, Ring, and Olson (1999, 2000) recognized the possibility of this genotype environment correlation and the need for more reading practice, particularly accurate reading practice, in many children with reading disabilities. They also noted that most of these children had phoneme awareness and phonological decoding deficits that were even worse than expected from their level of word recognition (Rack, Snowling, & Olson, 1992). These phonological deficits can compromise children's ability to read independently with sufficient accuracy to promote the kind of growth from reading practice that normal readers experience. Many teachers and clinicians recognize these special needs in children with reading disabilities, but the one-on-one or small-group tutorial resources that would be most helpful are often limited by teachers' time constraints in large classes and the cost of individual tutoring. Therefore, Wise et al. designed computer programs with speech feedback to support accurate word reading and comprehension of interesting stories that children with dyslexia could read independently on the computer. Other computer programs were designed to improve children's phonological awareness and phonological decoding skills.

The results from several of these studies were summarized by Olson and Wise (2006). They found that programs focused on phoneme awareness and phonological decoding substantially improved those skills. However, the pattern of results for growth in word recognition and spelling depended on children's initial reading level and grade. Children with reading disabilities in the second and third grades benefited more in spelling and in accurate reading of words from combined training in phonological skills and reading of stories on the computer. In contrast, fourth and fifth grade children with reading disabilities gained more in word recognition accuracy, fluency, and spelling from spending their training time accurately reading and comprehending stories on the computer. They achieved these greater gains in reading and spelling even though their growth in phoneme awareness and phonological decoding was significantly less than the group that split their training time between phonological skills and reading stories on the computer. Thus, accurate reading practice with interesting text at an appropriate instructional level may be the best intervention once children have reached a modest level of skill in phoneme awareness and phonological decoding, even if those skills are still significantly subnormal at the beginning of the intervention.

A new project in the current CLDRC, directed by Barbara Wise, will deploy newer versions of our earlier successful programs that are more visually engaging with better support for phonological skills

and independent reading practice. The programs will be deployed as early as mid-kindergarten in an RTI framework that includes systematic initial assessments for deficits in early reading skills, intervention to improve those skills, careful progress monitoring, and continued support for children who need it.

Long-term benefits from our computer-based training and other interventions for dyslexia may depend on improving children's motivation to read, an important factor in achieving the greater than normal amount of reading practice that many children may need to improve their reading percentile scores in the early grades, and maintain those gains through the later grades. Morgan et al. (in press) found that when they randomly assigned young children with reading disabilities to a small-group direct instruction intervention or a regular classroom control group, the modest but statistically significant superior growth of the intervention group did not result in significant improvement in either that group's motivation to read or their reading practice. This suggests that benefits of this intervention may not last through the later grades. The lack of improvement in motivation and reading practice led Morgan et al. to question the hypothesized causal direction from improved reading skills to improved motivation to read and more reading practice. They acknowledged, however, that stronger reading gains from more intensive interventions and other direct efforts to improve motivation and practice might yield better results.

Many members of the International Dyslexia Association (IDA) understand the importance of motivation and reading practice. IDA publications and conferences often recognize and honor the extraordinary effort that successful children and adults with dyslexia must expend to improve and maintain their reading and related skills. I have appreciated the occasional articles in IDA's *Perspectives* by students and adults with dyslexia who have described the hard work they did to overcome their difficulties in learning to read, often with the help of expert instruction and encouragement from their teachers, tutors, and parents. The day before my Geschwind lecture at the 2005 IDA meeting, I heard Greg Davis talk about his dedicated efforts and successes in dealing with his dyslexia (Davis & Davis, 2005). These personal accounts of successful children and adults with dyslexia testify to their determination and strength of character that may also account for their successes in other areas of life. Their stories should be told to all children who struggle with dyslexia.

Another reason that some with dyslexia may have great success in other areas of life is that dyslexia may sometimes be accompanied by remarkable natural talents and creativity in the arts and sciences (West, 2005). It was gratifying to see the award to John Horner for his outstanding work on dinosaur evolution and ecology that he received immediately preceding my lecture, and to hear his story in the Creative Brain symposium (Horner, 2005). It is clear that dyslexia and special talents can co-exist in these cases, and a dissociation between

specialized genes influencing brain development related to dyslexia and such special talents may have a role in their etiology.

Unfortunately, it appears that many children with reading disabilities have significant shared genetic influences on deficits in reading and a broad range of nonreading skills due to "generalist genes" described by Plomin and Kovas (2005). Some of these children may not meet the Reading-IQ discrepancy criteria that have traditionally been used to define dyslexia, but they show similar benefits from intervention for their deficits in word decoding skills, and they deserve our support in dealing with their learning difficulties (Lyon et al., 2001). I vividly remember attending a symposium on genius in dyslexia some years ago where a young man in the audience stood up and said something like ". . . What about me? I have no special genius. I have a hard time learning in all areas." A response from one of the panel members was something like, ". . . You just need to discover your special genius." The young man had a problem with that response, and so did I. He wanted to be recognized and valued for who he was and not for some fantasy about his special genius.

CONCLUSIONS

I believe that in the future, continued behavioral and molecular genetic research will lead us to more accurate early diagnosis, better interventions, and a better understanding of how risk alleles influence brain development in interaction with the environment for children with dyslexia. For the present, behavior genetic studies with twins have clearly demonstrated that there are strong average genetic influences on reading and other learning disabilities within the typical educational environments of children who are learning to read in their first language.

I believe that there are two important lessons to take from these results. First, most cases of dyslexia that occur within normal educational environments are not the fault of the child, their parents, their teachers, or their schools. Second, it is unrealistic to expect all children to reach "grade level" in reading or other academic skills, as the current No Child Left Behind legislation insists that they must, because some children have strong genetic or other biological constraints on their reading development. For some of the most severe cases of dyslexia, the most effective interventions might result in only modest but functionally significant gains. For example, they might move from the second percentile to the 15th percentile in reading. Although this is still well below "grade level," they are significantly better in their practical reading and related life skills than they were before the intervention. For this accomplishment, these children and those supporting their intervention should often be congratulated instead of being criticized for their failure in reaching an unrealistic goal.

Then maybe we can also do a better job of recognizing the basic human value and dignity of all children with learning disabilities who

are often neglected in our society. For example, an increase in the long stagnant minimum wage in the United States might be appropriate so that more children with significant learning disabilities and other less competitive members of our society will be better able to enjoy a decent life. The moral philosopher John Rawls (1976) in his *A Theory of Justice* asks us to imagine the type of society we would design if we knew we would have to enter it with no control over our genes or our environmental circumstances. We would simply be randomly assigned to our fate within the full range of those circumstances. Might we then reflect on the unfairness of this situation? Might we then design a society that would better protect us from the results of potential genetic and environmental misfortunes from the luck of the draw?

Obviously, I have wandered away here from the basic science of genetic and environmental influences on dyslexia that was the main focus of my lecture, and it is past time to close. Thanks for listening, and thanks for your good work on behalf of children with dyslexia and other learning disabilities.

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