Chapter • 3

Colorado Reading Project An Update

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In 1984 the National Institute of Child Health and Human Development (NICHD) sponsored a conference entitled "Biobehavioral Measures of Dyslexia." In a preface to the published proceedings of this conference, Gray and Kavanagh (1985) noted that: "Because the NICHD is currently supporting one collaborative interdisciplinary research project with a focus on reading, the Colorado Reading Project, this project served as one of the cornerstones for the development of the conference (p. x)." Since 1979, research at the University of Colorado concerning the etiology of reading disability had been supported in part by a program project grant from the NICHD. During the NICHD conference, co-investigators associated with the Colorado Reading Project summarized results obtained during its first five years. DeFries (1985) reviewed the background of the Colorado Reading Project and presented results of family, longitudinal, and risk analyses. Olson (1985) evaluated the component processes in reading and spelling, especially with regard to phonological and orthographic coding deficits in reading-disabled children. Decker and Vandenberg (1985) reviewed preliminary data obtained from a twin study of reading disability, and Shucard et al. (1985) described findings obtained from electrophysiological studies of cerebral functional specialization in disabled and normal readers.

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To date, the Colorado Reading Project has received continuous NICHD support for over ten years. The long-range objectives of this program project remain the identification, characterization, and validation of distinct subtypes or dimensions of reading disability. To accomplish these objectives, a test battery that includes measures of cognitive abilities and of reading and language processes is being administered to a sample of identical and fraternal twin pairs in which at least one member of each pair is reading disabled, to parents of these twins, to members of identical and fraternal twin families in which the children are normal readers, and to a longitudinal sample of nontwin reading-disabled and control children. Resulting twin and family data are being used to validate alternative typologies or dimensions of reading disability and to conduct genetic, longitudinal, and risk analyses. In addition, a survey of immune disorders and laterality is being administered to the twin sample, and data from program project families who manifest apparent autosomal dominance for reading disability are being subjected to linkage analysis using state-of-the-art genetic markers, including DNA restriction fragment length polymorphisms.

For administrative and logistical convenience, the Colorado Reading Project currently includes four substantive components: Twin/Family Study; Reading and Language Processes; Epidemiology of Immunological Differences; and Linkage Analysis. The primary objective of the present report is to summarize the results of recent research conducted within each of these components.

TWIN/FAMILY STUDY

In order to assess the genetic etiology of reading disability, a twin study was initiated in 1982 as part of the Colorado Reading Project. Administrators and school personnel in a total of 27 different school districts within the State of Colorado currently participate in this study. Without regard to reading status, all twin pairs within each district are identified and permission is then sought from parents to review the school records of both members of each pair for evidence of reading problems. If either member of a twin pair manifests a positive history of reading problems (e.g., low reading achievement test scores, referral to a reading therapist because of poor reading performance, reports by classroom teachers or school psychologists, etc.), both members of the pair are invited to complete an extensive battery of tests in our laboratories at the Institute for Behavioral Genetics and Department of Psychology, University of Colorado, Boulder.

In the laboratory of J. C. DeFries, an extensive psychometric test battery that includes the Wechsler Intelligence Scale for Children–

Revised (WISC–R; Wechsler 1974) or the Wechsler Adult Intelligence Scale–Revised (WAIS–R; Wechsler 1981) and the Peabody Individual Achievement Test (PIAT; Dunn and Markwardt 1970) is administered to the twins. In the laboratory of R. K. Olson, a battery of tests, including measures of phonological and orthographic coding, experimental measures of word recognition and reading comprehension, and measures of eye movements, is also administered to both members of each twin pair. Employing discriminant weights estimated from an analysis of PIAT Reading Recognition, Reading Comprehension, and Spelling data obtained from an independent sample of 140 reading-disabled and 140 control nontwin children (DeFries 1985), a discriminant function score is then computed for each subject. In order for an individual to be diagnosed as reading disabled in this component of the program project, the person must have a positive school history for reading problems and also be classified as affected by the discriminant score. Additional diagnostic criteria include an IQ score of at least 90 on either the Verbal or Performance Scale of the WISC or WAIS; no evidence of neurological, emotional, or behavioral problems; and no uncorrected visual or auditory acuity deficits.

A comparison group of control twins is also tested. Control twin pairs are matched to probands on the basis of age, gender, and school district. In order for a twin pair to be included in the control sample, both members of the pair must have a negative school history for reading problems and at least one member must be classified as unaffected by the discriminant analysis.

Selected items from the Nichols and Bilbro (1966) questionnaire are used to determine zygosity of same-sex twin pairs. In ambiguous cases, zygosity of the pair is confirmed by analysis of blood samples. As of December 31, 1989, a total of 99 pairs of identical (monozygotic, or MZ) twins, 73 pairs of same-sex fraternal (dizygotic, or DZ) twins, and 39 pairs of opposite-sex DZ twins meet our criteria for inclusion in the proband sample (i.e., at least one member of the pair of twins is reading disabled). In addition, a total of 99 pairs of MZ twins, 68 pairs of same-sex DZ twins, and 16 pairs of opposite-sex DZ twins compose the current control sample. These twins ranged in age from 8 to 20 years at the time of testing and all were reared in English-speaking, middle-class homes.

In contrast to the referred sample of nontwin reading-disabled children in which the gender ratio was 3.8 males to each female (DeFries 1985), the numbers of reading-disabled males and females in the current twin sample are 147 and 153, respectively. Because female MZ pairs tend to be overrepresented in twin studies (Lykken, Tellegen, and DeRubeis 1978), this lower gender ratio for reading-disabled members of twin pairs included in the Colorado Reading Project may be due

in part to a differential volunteer rate of male and female twin pairs. In accordance with this expectation, the gender ratio in the sample of MZ probands is somewhat lower than that for DZ probands: 68 MZ males, 84 MZ females, 79 DZ males, and 69 DZ females. However, neither gender ratio deviates substantially from equality (viz., 0.81 versus 1.15, respectively). In addition, Vogel (1990) notes that referred samples of learning-disabled children may not be representative of learning-disabled children in the general population. Thus, the excess of male subjects invariably found in system-identified populations of reading-disabled children may be due at least in part to a referral bias.

Twin Concordance Rates

Previous twin studies of reading disability (Zerbin-Rüdin 1967; Bakwin 1973; Stevenson et al. 1987) employed a comparison of concordance rates as a test for genetic etiology. Although the concordance rate for MZ twin pairs exceeded that for DZ pairs in each of these three relatively small studies (14–31 pairs of MZ twins and 27–42 pairs of DZ twins), substantial variation in concordance rates occurred among the studies. Results obtained by Zerbin-Rüdin (1967) and Bakwin (1973) suggest that reading deficits may be highly heritable, whereas those of Stevenson et al. (1987) indicate substantially less genetic influence. (For a more detailed review of previous twin studies of reading disability and the estimation of concordance rates, see DeFries and Gillis in press.)

The number of reading-disabled twin pairs tested to date in the Colorado Reading Project exceeds the total number of affected pairs in all previous studies. Therefore, the results of this single study warrant considerable confidence. The probandwise concordance rate for 99 MZ twin pairs tested in the Colorado Reading Project is 70%, whereas that for 112 DZ twin pairs is 48%. These results confirm the evidence for at least some genetic etiology of reading disability obtained in previous twin studies.

Multiple Regression Analysis of Twin Data

Although a comparison of concordance rates as a test for genetic etiology is appropriate for categorical variables such as presence or absence of an illness, reading disability is operationally defined (Wong 1986; Stevenson et al. 1987) and its diagnosis is made on the basis of arbitrary cut-off points along a continuous dimension (e.g., reading performance). Transformation of a continuous measure into a categorical variable (e.g., reading disabled versus normal) obviously results in a

loss of information pertaining to the continuum of variation in reading performance.

DeFries and Fulker (1985) recently proposed a methodology that facilitates an analysis of the etiology of deviant scores as well as individual differences within the proband group. In contrast to a comparison of concordance rates in MZ and DZ twin pairs, a comparison of MZ and DZ cotwin means was advocated as a test for genetic etiology. As illustrated in figure 1, when probands have been ascertained because of deviant scores on a continuous measure such as reading perfor-

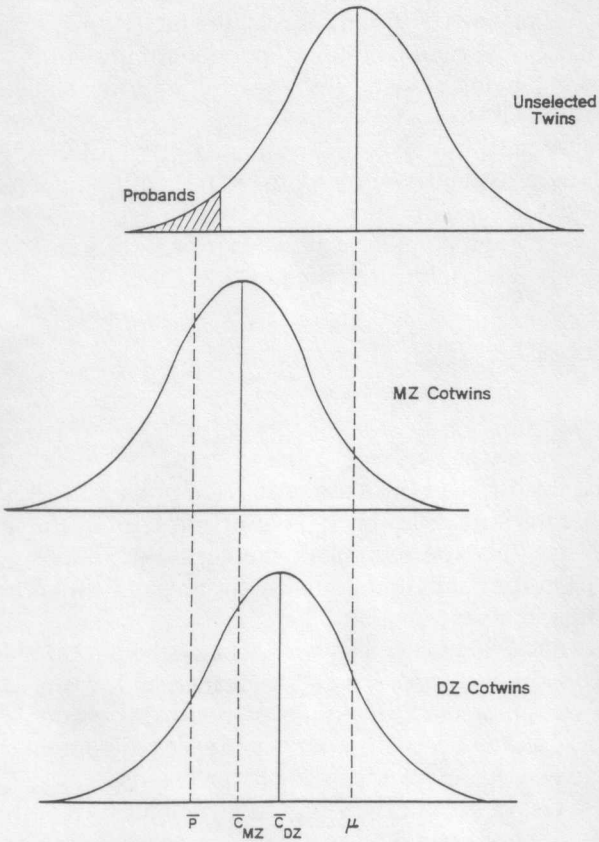

Figure 1. Hypothetical distributions for reading performance of an unselected sample of twins, and of the identical (MZ) and fraternal (DZ) cotwins of probands with a reading disability. The differential regression of the MZ and DZ cotwin means toward the mean of the unselected population (μ) provides a test of genetic etiology. From Evidence for a Genetic Aetiology in Reading Disability of Twins by J. C. DeFries, D. W. Fulker, and M. C. LaBuda, 1987, *Nature* 329:537. Copyright 1987 by Macmillan Journals Ltd. Reprinted by permission.

mance, the scores of both the MZ and DZ cotwins are expected to regress toward the mean of the unselected population. To the extent that the condition has a genetic etiology, however, this regression toward the mean should differ for MZ and DZ cotwins. Because members of MZ twin pairs are genetically identical, whereas members of DZ pairs share only about one-half of their segregating genes on average, scores of DZ cotwins should regress more toward the mean of the unselected population. Thus, if the MZ and DZ proband means are equal, a *t*-test of the difference between the means of the MZ and DZ cotwins would provide a test for genetic etiology. However, the partial regression of cotwin's score on the coefficient of relationship (R = 1.0 for MZ twin pairs and 0.5 for DZ twin pairs), independent of proband's score, provides a more general, statistically powerful, and flexible test (DeFries and Fulker 1985, 1988).

Two regression models were formulated: (1) a basic model in which the partial regression of cotwin's score on the coefficient of relationship provides a test for genetic etiology; and (2) an augmented model that also contains an interaction term between proband's score and relationships. These two models are as follows:

$$C = B_1P + B_2R + A \quad (1)$$

and

$$C = B_3P + B_4R + B_5PR + A, \quad (2)$$

where C is the cotwin's score, P is the proband's score, R is the coefficient of relationship, and PR is the product of proband's score and relationship. Because inclusion of the interaction term in the augmented model changes the expectations for the partial regression coefficients estimated from the basic model, the coefficients of P and R have different subscripts in equations 1 and 2.

DeFries and Fulker (1985) showed that B_1, the partial regression of cotwin's score on proband's score, is a measure of average MZ and DZ twin resemblance, whereas B_2 equals twice the difference between the means for MZ and DZ cotwins after covariance adjustment for any difference between scores of MZ and DZ probands. Thus, B_2 was advocated as a test of significance for genetic etiology. In addition, they demonstrated that B_3 and B_5 yield direct estimates of the proportion of variance due to environmental influences shared by members of twin pairs (c^2) and heritability (h^2), respectively.

DeFries and Fulker (1985) also noted that the results of fitting the basic model to selected twin data could be used to obtain an estimate of h^2_g, a measure of the extent to which the deficit of probands is due to heritable influences. In addition, it was suggested that a comparison of h^2_g and h^2 could be employed to test the hypothesis that the etiology of

extreme scores differs from that of variation within the normal range. Whereas the deficit of probands could be due to a major gene effect or to some gross environmental insult, for example, individual differences within the selected group might be due to multifactorial influences. If the etiology of deviant scores differs from that of variation within the normal range, h^2_g and h^2 would be expected to differ in magnitude. However, if probands merely represent the lower tail of a normal distribution of individual differences, h^2_g and h^2 should be of similar magnitude. More recently, DeFries and Fulker (1988) showed that a simple transformation of twin data (each score is expressed as a deviation from the mean of the unselected population and then divided by the difference between the proband and control means) prior to regression analysis facilitates a direct test of the hypothesis that the etiology of extreme scores differs from that of individual differences within the normal range. When MZ and DZ twin data are transformed in this simple manner, $B_2 = h^2_g$ and B_4 provides a significance test for $h^2_g - h^2$.

Because the probands in the Colorado Reading Project were selected on the basis of their discriminant scores (a composite measure of reading performance), the basic and augmented models were fitted to data for that measure. The average discriminant scores of the MZ and DZ probands and cotwins, expressed as standardized deviations from the control mean, are presented in table I. (Data from concordant twin pairs have been double entered for all analyses in a manner analogous to that used for computation of probandwise concordance rates.) From this table it may be seen that the average discriminant scores of the MZ and DZ probands are highly similar and over three standard deviations below the mean of the comparison sample of unaffected twins. In addition, it may be seen that the scores of the MZ cotwins have regressed only 0.25 standard deviation units on the average toward the control mean, whereas those of the DZ cotwins have regressed 0.95 standard deviation units. When the basic model was fitted to these data, $B_2 = -1.47 \pm 0.33$ ($p < .001$, one tailed). This highly significant coefficient is a function of the differential regression of the MZ and DZ cotwin scores and provides the best evidence to date for the heritable nature of reading disability.

Table I. Mean Discriminant Score of 99 Pairs of Identical Twins and 112 Pairs of Fraternal Twins in Which at Least One Member of Each Pair is Reading Disabled

	Probands	Cotwins
Identical	−3.13	−2.88
Fraternal	−3.05	−2.10

Note: Scores are expressed as standardized deviations from the mean score of 366 control twins.

In order to estimate h^2_g, the basic model was fitted to transformed discriminant function data. Because the means of identical and fraternal probands differ slightly, different transformations were employed for these two groups. When the basic model was fitted to these transformed data, $h^2_g = 0.47 \pm 0.11$ ($p < .001$). This highly significant parameter estimate suggests that about one-half of the reading performance deficit of probands, on average, is due to heritable influences.

When the augmented model was fitted to these transformed discriminant function data, $B_5 = h^2 = 0.73 \pm 0.36$ ($p < .01$, one tailed) and $B_3 = c^2 = 0.11 \pm 0.27$ ($p > .25$). These results suggest that individual differences within the selected group are highly heritable, whereas environmental influences that are shared by members of twin pairs are not an important source of variation. Moreover, although the estimates of h^2 and h^2_g are rather discrepant (0.73 and 0.47, respectively), suggesting that probands may not merely represent the lower tail of a normal distribution of individual differences, the difference between these two parameter estimates is not significant ($B_4 = -0.26 \pm 0.38$, $p > .25$).

Statistical Power

The multiple regression analysis of selected twin data provides a statistically powerful test of genetic etiology (DeFries and Fulker 1988). For example, when the basic model was fitted to transformed discriminant function data from the present sample of reading-disabled probands and cotwins, the estimate for $B_2 = h^2_g = 0.47$. The corresponding squared multiple correlation is 0.26, and the correlation between proband and cotwin scores is 0.43. Thus, the power (Cohen 1977) to detect a significant B_2 at the 0.05 level (one-tailed test) in a sample of 100 pairs of MZ and 100 pairs of DZ twins is 0.99.

Although the multiple regression test for genetic etiology is statistically powerful, the probability of rejecting the null hypothesis that $B_5 = h^2 = 0.0$ is no greater than that for estimates obtained from alternative twin analyses. For example, given the present data set in which $h^2 = 0.73$ and the corresponding squared multiple correlation (0.27), the power to detect a significant h^2 at the 0.05 level (one-tailed test) in a sample of 100 pairs of MZ and 100 pairs of DZ twins is 0.49. In a sample of 200 pairs of MZ and 200 pairs of DZ twins, the power increases to a more respectable 0.73.

Because the power to detect a significant h^2 is relatively low, the power to detect a significant difference between h^2_g and h^2 will be even lower. Given the data in the present sample in which $h^2_g = 0.47$ and $h^2 = 0.73$ and the associated squared multiple correlations, the power to detect a significant $B_4 = h^2_g - h^2$ at the 0.05 level (two-tailed test because

there is no a priori expectation regarding the direction of the difference) in a sample of 200 pairs of MZ and 200 pairs of DZ twins is less than 0.20. Thus, a larger sample of twins will be required to test more rigorously the hypothesis that the etiology of extreme scores differs from that of individual differences within the normal range. However, because such a test is of considerable interest, especially with regard to the issue of the specificity of the deficit in reading disability (Foorman 1989), additional testing of twins in the Colorado Reading Project is clearly warranted.

Differential Etiology

The multiple regression analysis of selected twin data is also a highly flexible methodology. The basic and augmented models can be easily extended to include other main effects and interactions (Cohen and Cohen 1975) to test for differential genetic and environmental influences (DeFries and Gillis in press; Olson et al. in press-a). Because the multiple regression test for genetic etiology is statistically powerful, the test for differential genetic etiology is also relatively powerful. For example, if h^2_g in two subtypes differed by 0.5, the power to detect a significant interaction between R and subtype at the 0.05 level (two-tailed test) in a sample of 100 pairs of MZ and 100 pairs of DZ twins would be about 0.75 (DeFries and Fulker 1988). If the difference in h^2_g between subtypes were only 0.3, the power would be only about 0.3. However, by increasing the sample size to 150 pairs of MZ twins and 150 pairs of DZ twins, the power would be increased to about 0.90 and 0.50 in these two cases.

Wadsworth, Gillis, and DeFries (1990) recently employed this methodology to test a hypothesis that the genetic etiology of reading disability may differ as a function of age (Stevenson et al. 1987). When the basic model was fitted separately to data from younger (8.3–14.0 years) and older (14.1–20.2) twin pairs, estimates of h^2_g were 0.49 ± 0.12 and 0.39 ± 0.24, respectively. Thus, these results are consistent with the hypothesis of Stevenson et al. (1987) that genetic factors may be less important as a cause of reading disability in older children. However, the difference between these two estimates was found to be nonsignificant ($p > .50$) when an extension of the basic model that included an interaction between group membership and relationship was fitted simultaneously to data from both the younger and older twin pairs. Application of a more powerful test of differential genetic etiology that included age and its interactions as continuous measures in a regression model also yielded a nonsignificant ($p > .50$) result. When the basic model was fitted to data from twin pairs divided into three age groups (8.3–12.5, 12.6–15.5, and 15.6–20.2 years), resulting

estimates of h^2_g were 0.48 ± 0.13, 0.26 ± 0.20, and 0.76 ± 0.40. Although this result suggests that genetic factors may be less important as a cause of reading problems during adolescence, a test for differential genetic etiology as a quadratic function of age was also nonsignificant. Thus, a more rigorous test of the hypothesis that the genetic etiology of reading disability differs as a function of age must also await the testing of additional twins in the Colorado Reading Project.

READING AND LANGUAGE PROCESSES

The focus of this component of the Colorado Reading Project is specific reading processes and related perceptual and language skills. The major goals are to evaluate profiles of component reading and language skills in reading-disabled and normal groups, to describe the range of individual differences within the reading-disabled population, and to assess the relative influence of genetic and environmental influences on deficits in specific reading processes and related cognitive skills. Progress in achieving these goals will be reviewed in three sub-sections. First, performance profiles will be compared for groups of younger normal readers and older disabled readers matched on level of word recognition. Second, the genetic etiologies of deficits in two specific components of word recognition will be compared. Third, differential genetic etiology of word-recognition deficits will be evaluated in relation to several subtype variables.

Disabled and Normal Profiles

Are there significant differences between disabled and normal readers' profiles of component reading and language skills, or are disabled readers equally depressed on all component reading and language skills? When disabled readers are compared with same-age normal readers, it is not surprising to find that the disabled readers are significantly lower on all reading and related skills. A number of researchers have argued that a more appropriate comparison of profile differences between disabled and normal readers can be obtained by matching older disabled and younger normal groups on a measure of reading (cf. Bryant and Goswami 1986).

Our reading-level-match comparisons of disabled and normal groups have used the PIAT word recognition test as the matching variable. From this reference point, it was found that the older disabled group (M = 15.6 years) was significantly better than the younger nor-

mal group (M = 10.4 years) on measures of reading comprehension (Conners and Olson in press). Results obtained from path analyses indicated that the disabled readers' superior performance on reading comprehension was related to their superior performance (in raw scores) on the Wechsler (1974, 1981) verbal subtests. Thus, by relying on their greater absolute level of verbal intelligence, the older disabled readers' comprehension of written text was better than would be expected from their very low ability in isolated word recognition. However, the disabled subjects' uniquely poor word recognition skills constrained their reading comprehension to levels substantially below that of normal readers at the same age and IQ.

The basis for disabled readers' poor word recognition has been a central focus of our research. Tasks were designed to measure subjects' skills in two component processes of word recognition, phonological coding, and orthographic coding (Olson et al. 1989). The phonological coding task required subjects to read aloud 85 nonwords of varying difficulty (e.g., int, tegwop, calch) as quickly and accurately as possible. The subject's score in this task was a composite of z scores for accuracy and speed on correct responses. Phonological coding is particularly important when readers encounter unfamiliar printed words. Recent evidence has indicated that phonological coding processes are also involved in the skilled reading of familiar words (Van Orden 1987).

The second component process in word recognition, orthographic coding, was measured by having subjects designate the word in 80 word-pseudohomophone pairs (e.g., rain, rane; salmon, sammon) as quickly as possible. The two letter strings in each pair were phonologically identical (i.e., they would sound the same if pronounced according to common phonological rules). Therefore, subjects had to recognize the specific orthographic pattern for the target word to make a correct choice. Scores on this task were based on the subject's combined z scores for accuracy and speed on correct responses. Orthographic coding is a particularly important process in reading English, which contains many homophones that must be discriminated (e.g., their, there), and many "exception" words that do not conform to common phonological rules (e.g., yacht, said). The theoretical background for the orthographic and phonological tasks is discussed in Olson et al. (in press-b).

When the older reading-disabled and younger normal groups matched on PIAT word recognition were compared on the phonological and orthographic tasks, a striking difference in profiles was observed (Olson et al. 1989). The disabled readers' performance on the orthographic task was slightly, but significantly, better than that of the younger normal group. In contrast, the disabled readers' performance

on the phonological coding task was 0.78 of a standard deviation below the mean for the younger normal group ($p < .01$). Thus, on average, disabled readers had phonological coding skills that were well below the levels expected from their word recognition.

These results replicated findings from an earlier study in the Colorado Reading Project that used different samples and measures of phonological and orthographic coding (Olson et al. 1985). However, the results of reading-level-match studies from other laboratories have been less consistent. Some have found a phonological deficit in disabled readers (cf. Snowling 1980), whereas others have reported that disabled readers' phonological coding was not significantly different from that of younger normal readers at the same level of word recognition (cf. Treiman and Hirsh-Pasek 1985). A recent meta analysis of reading-level-match studies on phonological coding concluded that most of the null results could be accounted for by factors such as ceiling effects, regression artifacts in sample selection, and inadequate assessment and control of IQ differences between the groups (Olson et al. in press-b; Rack, Snowling, and Olson submitted).

The best evidence indicates that most children who meet the usual selection criteria for specific reading disability have a unique problem in phonological coding. However, our disabled readers showed substantial within-group variance in phonological coding after adjustment for their level of word recognition. Much of this variance was related to the disabled readers' performance on a "pig latin" task that required segmental language skills. Disabled readers who were relatively good at this segmental language task were also relatively good in phonological coding (Conners and Olson in press).

The disabled readers' phonological coding was also related to within-group variance in verbal IQ. Earlier results from the Colorado Reading Project revealed a small, but significant, *negative* partial correlation ($r = -.28$, $N = 59$) between disabled readers' accuracy in oral nonword reading and their combined scores on four Wechsler subtests (Information, Vocabulary, Similarities, and Comprehension) that were included in Kaufman's (1975) verbal factor (Olson et al. 1985). (The partialed variable was PIAT word recognition.) Rack and Olson (1989) found a similar negative partial correlation ($r = -.29$, $N = 218$) between our current phonological coding measure and Kaufman's verbal factor in a much larger sample. These small negative correlations suggest that factors associated with low verbal intelligence may be contributing to low word recognition for some disabled readers in our sample. But for most disabled readers, poor phonological coding and related segmental language skills seem to be the major constraints on their development of word recognition. Behavioral genetic analyses reviewed in the following section indicate that disabled readers' heritable deficits

in word recognition are strongly related to their heritable deficits in phonological coding.

Behavioral Genetic Analyses

The genetic etiology of disabled readers' deficits in word recognition, phonological coding, and orthographic coding was examined by Olson et al. (1989) using the regression model developed by DeFries and Fulker (1985). The difference between MZ and DZ cotwins' regression toward the normal mean yielded an estimate of the degree to which the probands' group deficit was heritable (h^2_g). When the basic model (equation 1) was fitted to word recognition data from 117 twin pairs, $h^2_g = 0.40 \pm 0.12$, ($p < .01$), indicating that about 40% of the probands' deficit was due to heritable influences. Corresponding estimates of h^2_g for phonological and orthographic coding deficits were 0.47 ± 0.14 and 0.28 ± 0.16, respectively. Thus, the phonological coding deficits of reading-disabled children are significantly heritable, whereas their orthographic coding deficits are not.

Additional analyses assessed the genetic covariance between subjects' deficits in word recognition and their deficits in phonological and orthographic coding (Olson et al. 1989). Genetic covariance is an index of the degree to which genetic variance in one variable is shared with that in another variable (Plomin, DeFries, and McClearn 1990). Because subjects were selected for word-recognition deficits in this analysis, the h^2_g of correlated variables estimates the genetic covariance between word recognition and the correlated variable divided by their phenotypic covariance, i.e., a measure of the extent to which the observed association is due to genetic influence. Resulting estimates of h^2_g for phonological and orthographic coding were 0.93 ± 0.16, and -0.16 ± 0.27, respectively, suggesting a substantial genetic covariance between word recognition and phonological coding.

Our most recent unpublished analyses with a much larger sample (284 pairs of twins) confirm the above pattern of differential heritabilities and genetic covariance for word recognition, phonological coding, and orthographic coding. Estimates of h^2_g for word-recognition deficits (0.54 ± 0.08), phonological coding (0.54 ± 0.10), and orthographic coding (0.28 ± 0.11) are slightly higher than the previously reported estimates (Olson et al. 1989). For the genetic covariance analysis, a bivariate form of the basic model was employed in which the cotwins' scores for either phonological or orthographic coding were predicted from the word recognition scores of probands. The resulting "bivariate h^2_g" estimates the genetic covariance between word recognition and the correlated variable, divided by the phenotypic variance of word recognition. Thus, a comparison of the two bivariate h^2_g estimates in-

volving phonological and orthographic coding provides a direct test of their differential genetic covariance with word recognition. As in our previous analyses, the bivariate h^2_g estimate between word recognition and phonological coding (0.81 ± 0.14) is substantially higher than between word recognition and orthographic coding (0.27 ± 0.18). The difference between these two estimates is statistically significant ($p < .05$) when tested in a LISREL model.

The above results clearly indicate a strong genetic influence on deficits in word recognition, primarily through heritable deficits in phonological coding. However, the path of genetic influence on phonological coding may ultimately be through heritable differences in segmental language skills. Olson et al. (1989) reported significant genetic covariance between deficits in phonological coding and the "pig-latin" task discussed earlier ($h^2_g = 0.81 \pm 0.38$), and between phonological coding and a rhyme-generation task ($h^2_g = 0.99 \pm 0.43$). Further research is underway to confirm this relation with additional measures of segmental language skills.

The low heritability and genetic covariance estimates for orthographic coding indicate that this skill is predominantly influenced by environmental factors. Stanovich and West (1989) found that indirect measures of reading experience accounted for significant variance in measures similar to our orthographic coding task, after partialing variance in phonological coding. Shared home and school environments for print exposure in our MZ and DZ twin pairs may thus be responsible for the significant c^2 (shared environment) estimates that we are finding for individual differences in orthographic coding (but not phonological coding) within the disabled and normal groups.

Differential Heritability of Word-Recognition Deficits

Our estimates of h^2_g for word recognition are estimates of the heritability for the *group* deficit. It is possible that there are systematic differences in h^2_g within the disabled group that are related to subtype variables. In the first section of this chapter there was a discussion of the differential heritability of disabled subjects' discriminant scores depending on age (Wadsworth, Gillis, and DeFries 1990). The same model used in that analysis has been applied to evaluate differences in h^2_g for word recognition as a function of deficit severity, phonological coding, orthographic coding, IQ, gender, and age (Olson et al. in press-a).

Severity of word-recognition deficits was the subject of our initial subtype analysis. There was a continuous distribution of word-recognition deficits below the cutoff score of one standard deviation

(*SD*) below the mean of the normal control group. Therefore, the significance test for differential h^2_g was based on its linear relation to the severity of word-recognition deficits. The test was statistically significant ($p = .045$). The magnitude and direction of this differential heritability was indicated by a separate assessment of h^2_g for groups divided at the mean word-recognition deficit of -2.4 *SD*. For 85 twin pairs whose proband was below the group mean deficit of -2.4 *SD* (subgroup mean = -3.31 *SD*), $h^2_g = 0.51 \pm 0.11$. For 105 pairs above the group mean deficit (subgroup mean = -1.68 *SD*), $h^2_g = 0.80 \pm 0.17$. These results thus indicate significantly higher heritability for *less* severe deficits in word recognition. We have examined the twins' birth and medical information provided by the parents to determine if environmental insults might have lead to the more severe deficits in word recognition. Birth and medical problems were rare and their prevalence was not significantly different between the more and less severe subgroups (Olson et al. in press-a). We are now exploring other possible explanations for the differential etiology of more and less severe reading deficits.

The above differences in h^2_g as a function of deficit severity in word recognition complicate the analysis of other subtype variables that are correlated with word recognition. Therefore, we adjusted the orthographic coding, phonological coding, and IQ variables for their relation to word recognition before using those variables as subtype dimensions. Differential h^2_g of word recognition as a function of differences in phonological coding (adjusted for word recognition) approached statistical significance ($p = .057$). For 86 pairs who were lower than the mean adjusted phonological coding score, $h^2_g = 0.74 \pm 0.15$. For 104 pairs above the mean, $h^2_g = 0.54 \pm 0.11$. Thus, subjects who were relatively poor phonological coders, compared to their word recognition, tended to have higher heritabilities for their deficits in word recognition. This result is consistent with the high genetic covariance between word recognition and phonological coding that was discussed earlier. Environmental factors such as reading experience may play a greater role in the word-recognition deficits of the better phonological coders.

None of the other subtype variables approached statistical significance for predicting differential h^2_g of disabled readers' word recognition. However, there was an interesting trend in relation to IQ. After phonological coding, the next highest level of statistical significance for differential h^2_g involved full-scale IQ ($p = .17$). For this analysis, 30 twin pairs who did not meet the minimum verbal or performance IQ criterion of 90 were added to the sample to increase the IQ range. For 123 pairs whose mean IQ was 91, $h^2_g = 0.40 \pm 0.10$. For 124 pairs whose mean IQ was 107, $h^2_g = 0.67 \pm 0.11$. This trend suggests that the heritability for word-recognition deficits is higher for subjects whose IQ

is high relative to their word recognition ability. Although the word-recognition deficits of subjects with lower IQ are significantly heritable, environmental influences may be relatively more important as a cause of reading disability in these subjects. Confirmation of these trends and marginally significant results for differential h^2_g will require a larger twin sample.

In summary, the behavioral genetic analyses in the Reading and Language Processes component of the Colorado Reading Project have yielded evidence for a significant genetic covariance between word-recognition deficits and phonological coding. In contrast, the relationship between word recognition and orthographic coding appears to be due largely to environmental influences. New measures of segmental language skills, visual processes, and reading experience have recently been added to the test battery to explore further the origins of genetic and environmental influences on word recognition and its component coding skills.

EPIDEMIOLOGY OF IMMUNOLOGICAL DIFFERENCES

The focus of this component of the Colorado Reading Project is on the clinical correlates of reading disability (dyslexia) and their relation to its etiology. Like other complex behavioral disorders, reading disability has a number of clinical correlates, some with a straightforward relation to its primary symptoms and others not so straightforward. One of the goals of research on subtypes of reading disability is to determine which putative clinical correlates are causally related either to reading disability in general or to one of its subtypes. The twin method employed in the Colorado Reading Project provides a powerful method of testing the validity of such subtypes defined in terms of clinical correlates. Specifically, the twin method permits several different validity tests, including tests of differential genetic etiology, genetic covariance, and cross-concordance.

For example, if subtypes are defined dichotomously (such as dyslexics with and without attention deficit hyperactivity disorder–ADHD), then the extended regression model described in the Twin/Family Study section of this chapter can provide a direct test for the differential genetic etiology of reading deficits in the two subtypes (see also LaBuda, DeFries, and Pennington 1990; Olson et al. in press-a). If differential heritability is found, that result validates the typology because it suggests differential genetic etiology for each subtype. Null results, as usual, are not conclusive because they may result from lack of power or from genetically distinct mechanisms (e.g., polygenic versus recessive) that are nonetheless essentially equal in their heritability.

If the subtype is defined using a continuous measure (such as rat-

ings of ADHD), then the genetic covariance between reading measures and the continuous measure of the comorbid condition can be evaluated. This analysis provides an indirect estimate of whether there is a genetic correlation between the two dimensions. If the results are significant, then there is evidence that the same genetic factors influence both dimensions of performance. For instance, the results of Olson et al. (1989) indicate that there is a significant genetic covariance between word-recognition deficits and phonological coding, and that there is a common genetic etiology for reading disability and what many regard as its proximal cause, a deficit in phonological coding.

Cross-concordance analyses address the issue of genetic correlation using categorical measures, such as presence or absence of RD or ADHD, and can be applied either to the sample as a whole or to a subset of probands who have both disorders (e.g., RD + ADHD). When applied to the whole sample, a cross-concordance analysis examines whether the rates of the second disorder (e.g., ADHD) are significantly higher in the MZ versus DZ cotwins of probands who have the first disorder (e.g., RD). If so, there is evidence in the sample as a whole for a common etiology for the two disorders. The result of this analysis could conceivably differ from the result of the genetic covariance analysis discussed above, since the etiology of extreme scores on a dimension may vary from the etiology of variation on the whole dimension. Cross-concordance analysis of a subtype (e.g., RD + ADHD) examines the possibility that the disorders have a common etiology in a subtype, whether or not they do in the whole sample.

Clinical correlates of reading disability ostensibly include immune disorders (Geschwind and Behan 1982, 1984). We tested this apparent association in our extended family linkage sample and (to our surprise) replicated it (Pennington et al. 1987). Specifically, we found increased rates of both autoimmune and allergic disorders, but not comparison disorders (stuttering, migraines, or diagnosed ADHD), in familial dyslexics relative to the prevalence of these disorders in either nondyslexic relatives or in the general population. However, we failed to find any association between dyslexia and non-right handedness, contrary to the neurobiological theory proposed by Geschwind and Galaburda (1985). Since the extended family linkage sample is a highly selected sample of dyslexic families (large, extended dyslexic families with a three-generation history of dyslexia—see Linkage Analysis section below), we felt it was important to assess the association between reading disability and immune disorders in a more representative population. Accordingly, we obtained data on the rates of immune and comparison disorders in the families of twins tested in the Colorado Reading Project. The use of twin samples also permitted a direct test of the cross-concordance of reading disability and immune disorders.

To examine the relation between reading disability and immune

disorders in the twin samples, we obtained self-report data on immune and comparison disorders by mail questionnaires from 176 reading-disabled (RD) and 113 control twin families. These samples represent 83% and 66% of the program project samples, respectively. Rates for these disorders for individuals in RD versus control families and for RD versus non-RD individuals are given in table II. (These rates are adjusted for sex, since the sex ratios vary across groups; sex adjustment did not change the results.) As can be seen, these results appear to provide a clear non-replication of our earlier results. In fact, there were significantly higher rates of allergic disorders ($\chi^2 = 7.52$, $df = 1$, $p < .01$) and migraines ($\chi^2 = 5.46$, $df = 1$, $p < .05$) in the non-RD relatives of RD twins. These results suggest that an underlying factor could lead to reading disability in some relatives and to allergy or migraines in others, but it does not support the hypothesis that reading disability and immune disorders cosegregate in the same individuals. Either there is no cosegregation between reading disability and immune disorders or the cosegregation found earlier is true for only a small subtype of dyslexic families, which is not detectable in an analysis of the whole population. Another logical, but unlikely, possibility is that the association is present only in non-twin RD families.

To test the possibility of a subtype of dyslexia with immune disorders, we next examined the pairwise cross-concordance of reading dis-

Table II. Immune Disorders and Reading Disability

		Immune Disorders			Comparison Disorders		
	N	Allergic	Asthma	Auto	Stutter	Hyper	Migraines
				Families			
RD Families (M/F = 1.05)	1044	20.1	9.2	5.3	2.5	2.0	9.2
Control Families (M/F = 0.90)	692	21.6	10.5	6.3	1.9	0.6	7.6
				Individuals			
RD (M/F = 1.05)	299	19.5	8.6	3.4	3.0	4.4	6.1
Non-RD Relatives (M/F = 0.95)	259	28.9**	10.3	3.6	2.4	1.3	11.2*
Non-RD Controls (M/F = 0.69)	325	23.8	10.7	4.6	1.5	0.8	8.1

* $p < .05$.
** $p < .01$.

ability and immune disorders in the twin samples. (Analyses employing probandwise concordance rates yielded similar results.) A genetic etiology for reading disability already has been well established in this sample (see Twin/Family Study section). Likewise, as shown in table III, we found evidence for genetic etiology of atopic disorders (allergy plus asthma), $\chi^2 = 28.19$ ($p < .001$). The critical question was whether reading disability and atopic disorders were genetically correlated in all or some of this sample. This issue was examined by computing the cross-concordance in MZ versus DZ pairs, beginning with a proband affected by reading disability and examining the rates of allergy/asthma in the cotwins. Null results were obtained (table III), paralleling the null results for the association of dyslexia and immune disorders in the entire twin sample. Likewise, null results were obtained when we began with a proband with allergy/asthma and examined the rates of dyslexia in the cotwin. We clearly rejected the hypothesis of genetic correlation in the entire sample, but the hypothesis of a genetic subtype remained to be tested.

In this analysis we selected twin probands who were affected with *both* dyslexia and allergy/asthma and examined the cotwins' status for both diagnoses (table IV). As can be seen, there is evidence for a genetic correlation in this subtype, because the MZ concordance rate for this subtype is significantly higher than the DZ concordance rate. However, since there are high rates of both dyslexia and self-reported immune disorders in these samples, and since each of these disorders is heritable, the significantly greater MZ concordance for the subtype might be an artifact. We next performed a series of analyses to test this possibility.

Several alternative methods may be employed to correct the twin concordance rates for base rate. One method assumes population base rates for dyslexia (e.g., 7.5%) and allergy/asthma (e.g., 13%), and uses their cross-product to derive expectancies for having the two disorders

Table III. Concordance and Cross-Concordance of Allergy/Asthma in Total Sample

	Number of Pairs	Concordant	Discordant
Pairwise Concordance of Allergy/Asthma in RD and Control Twins			
MZ	52	40 (0.77)	12 (0.33)
DZ	73	21 (0.29)	52 (0.71)
Pairwise Cross-Concordance of Reading Disability and Allergy			
MZ	59	20 (0.34)	39 (0.66)
DZ	41	16 (0.39)	25 (0.61)

Note: These are pairwise analyses. Similar results are obtained when probandwise analyses are performed.

Table IV. Cross-Concordance of Reading Disability Plus Allergy/Asthma Subtype

	Pairs	Concordant	Discordant (1 + 2 + 3)
MZ	20	13 (0.65)	7 (0.35)
DZ	27	3 (0.11)	24 (0.89)
			$\chi^2 = 16.79, p < .001$

Note: Concordant = Both twins have RD and allergy/asthma; Discordant1 = one twin has both and the co-twin has RD but no allergy/asthma; Discordant2 = one twin has both and the co-twin has allergy/asthma but no RD; Discordant3 = one twin has both and the co-twin has neither allergy/asthma nor RD.

by chance alone. This gives a small expected frequency for RD with AD of roughly 1%, and, when applied to the data in table IV, results in a highly significant chi-square. If we use the higher base rates for the two conditions that we obtain from our control sample, the chi-square is still highly significant. The problem with these two types of correction is that they fail to account for the heritability of each condition, which leads to a higher expected percent of concordant MZs than concordant DZs.

The method that takes both population (for at least our sample) prevalence rates and heritabilities into consideration involves obtaining base rates for MZ and DZ concordances independently. Details of how to obtain these base rates are given in Gilger, Pennington, and DeFries (in review). These MZ and DZ concordance rates for reading disability were 60% and 46%, and for allergy/asthma they were 73% and 29%, respectively. Thus, if we assume that RD and AD are independently transmitted, then the expected MZ concordance for RD + AD equals 44% (60% × 73%). For DZs the expected concordance rate is 13%. Applying a chi-square goodness of fit analysis to the data in table IV reveals that the differences between observed and expected concordance rates are marginally significant ($\chi^2 = 3.66, 1\,df, p < .07$). Further study of the observed frequencies in table IV shows that the significant chi-square is solely due to the fact that the MZ concordance rate is higher than expected if the two disorders are indeed independently heritable in the RD + AD proband twin pairs. The DZ rates are in fact identical to expectations. Given the manner by which expected values were calculated, we consider this test of differential concordances to be fairly conservative.

A remaining problem with our cross-concordance analysis is that currently it is based on a relatively small sample. Nevertheless, these preliminary results are convergent with preliminary results from the Linkage Analysis component indicating a subtype of familial dyslexia closely linked to the HLA region of chromosome 6, which contains many genes that affect the immune system. There may be a gene in this region that affects both reading and immune functions or, alter-

natively, there could be two closely linked genes that are independent in their pathophysiologies. Clearly more work is needed to validate the existence of a subtype of dyslexia associated with immune disorders and to understand the neurobiological mechanisms underlying this subtype.

LINKAGE ANALYSIS

Almost from the time reading disability first was described in the medical literature, early case reports and family studies led to the conclusion that it was inherited as an autosomal dominant condition (Hallgren 1950). More recent studies demonstrated that there probably is more than one mode of transmission (Finucci et al. 1976; Lewitter, DeFries, and Elston 1980), including autosomal dominant, autosomal recessive, and multifactorial inheritance. Localization and characterization of such genes would be of great value in understanding the mechanism of genetic influence on the reading process, which presumably could contribute to more effective therapy. Linkage analysis is a technique for localizing such genes along the chromosomes.

Linkage analysis has been used mainly to localize single major genes (often referred to as "Mendelian," in that the phenotypes are discrete and exhibit fairly clear recessive or dominant inheritance patterns), but the potential for localization of genes influencing quantitative traits has been recognized (Haseman and Elston 1972). With the advent of restriction fragment length polymorphisms (RFLPs) and the resulting explosion of markers all along the chromosomes, there has been increasing interest in using linkage analysis to examine conditions that may be due to more than one gene, either individually or in combination (Lander and Botstein 1986, 1989).

Linkage analysis is based on the fact that genes that are close together on the same chromosome tend to be inherited together as they are passed on from parent to child. Genes that are far apart on the same chromosome or on different chromosomes show random assortment as they are transmitted from generation to generation; that is, the probability that a child will inherit a specific allele is not influenced by the inheritance of the alleles at the other locus. If the inheritance pattern of the alleles from the two genes deviates significantly from random, this is taken as evidence that the genes are close together (linked). In practice, to localize a gene, its transmission is compared to the transmission of a battery of "marker" genes whose location is known; if linkage is found between the gene and one of the markers, the gene is localized to the chromosomal region of the marker. The distance between the gene and the marker can be estimated by the percentage of time the

two alleles are not inherited together. This is termed recombination, and is due to crossing over between paired chromosomes in the region between the two loci. The frequency of recombination (expressed as θ) increases as the distance between genes increases. The probability that linkage exists, given a specific value of θ, can be expressed as a LOD score, the *L*og of the *Od*ds of linkage. By convention, a LOD score greater than 3.0 is taken as evidence for linkage, and a LOD score less than -2.0 rejects linkage at that value of θ (Morton 1955). Evidence for genetic heterogeneity is obtained when linkage is demonstrated clearly in some families, but data from other families reject that linkage or support an alternate linkage (Morton 1956).

Previous linkage analysis with reading disability had suggested that it may be linked to the short arm/centromere heteromorphisms of chromosome 15 in some families (Smith et al. 1983). Subsequent studies have been designed to confirm that potential localization with DNA polymorphisms on chromosome 15, since these would provide additional and more easily replicated markers. Also, genetic heterogeneity was suspected, based on the wide range of the LOD scores from different families as well as theoretical expectations that a complex disability such as reading can be caused by more than one genetic factor. In addition to using statistical methods to test the LOD scores from chromosome 15 markers for homogeneity, markers from one other chromosome have been examined to see if there is suggestion of an alternate linkage, particularly in families clearly not showing linkage to chromosome 15. Based on pilot studies done using traditional genotyping markers, the Bf and GLO loci on chromosome 6 were chosen for further study. These loci are also intriguing since they are within the HLA region, which may have some bearing on the immunological variations suspected in disabled readers (Geschwind and Behan 1982; Pennington et al. 1986). A total of 22 families of children with reading disability has now been studied.

Present Sample

Families were selected from clinical populations in Denver and from the Colorado Reading Project. Initial selection criteria were an apparent extended family history of specific reading disability on one side of the family, following an apparent autosomal dominant pattern, and both biological parents and at least two children over 7 years of age available for study. All families were native English speaking and of middle-class background, and all family members in the study had a Verbal or Performance IQ of at least 90. A battery of tests was administered to each family member to confirm the history of the presence or absence of specific reading disability.

The definition of specific reading disability was the existence of significant difficulty in the tests measuring reading and spelling, with normal abilities in other academic areas. This diagnosis was made based on three factors: (1) Reading Quotient (RQ) (Finucci 1978); (2) the Specific Dyslexia Algorithm (SDA) as developed by Pennington, which specifies a pattern of high achievement in Mathematics and General Information, lower achievement in Reading Comprehension, and lowest in Reading Recognition and Spelling (Pennington et al. 1984); and (3) an early history of significant and persistent problems learning to read, without known etiology. From these criteria, five different categories were defined: affected (positive RQ or SDA and positive history); unaffected (negative RQ, SDA, and history); compensated (negative RQ and SDA, positive history); obligate carrier (negative RQ, SDA, and history, but with an affected child and affected sibling or parent); and questionable (anything other than the above; for example, positive RQ but negative history). For the linkage analysis, compensated individuals and obligate carriers were considered affected, and questionable individuals were omitted.

Blood samples were taken from all participating family members for typing of the traditional genotyping markers, chromosomal heteromorphisms, and DNA restriction fragment length polymorphisms. Informative family members have been typed for chromosomal variates and the DNA polymorphisms D15S1 (pDP151), D15S2 (pMS1-14), D15S3 (pJu201), D15S24 (CMW1), and TH114. Families were also typed and analyzed for three loci on chromosome 6: BF (properdin factor), GLO1 (glyoxylase I), and 2C5 (D6S8). Two forms of linkage analysis were performed: two-way, in which loci are examined two at a time; and multipoint, in which information from several markers is used simultaneously. The computer program LINKAGE (Lathrop et al. 1985) was used for these analyses, with reading disability represented as a fully penetrant, autosomal dominant, dichotomous trait. The resulting LOD scores were tested for homogeneity of the recombination fraction with HOMOG (Ott 1985).

Two-Way Analysis

The results of the two-way analysis with reading disability and chromosome 15 heteromorphisms are shown in table V. The maximum LOD score is 1.328 at a recombination level of 30%, which is inconclusive evidence for linkage. However, a wide range of LOD scores between families is observed, and, in particular, Family 6432 has a LOD score of 2.907 with no recombination. Since other families have clearly negative LOD scores, this suggests that heterogeneity may be present.

In testing for homogeneity of the LOD score data, the program

Table V. Linkage between SRD and Chromosome 15 Heteromorphisms

	Recombination Fraction				
	0.00	**0.10**	**0.20**	**0.30**	**0.40**
Family					
9007	$-\infty$	−0.389	−0.051	0.030	0.019
9008	$-\infty$	−0.267	−0.110	−0.049	−0.014
9102	$-\infty$	−0.957	−0.425	−0.168	−0.039
6372	$-\infty$	−0.350	0.164	0.276	0.201
6375	0.628	0.535	0.370	0.191	0.051
6432	**2.907**	**2.401**	**1.877**	**1.323**	**0.712**
6484	$-\infty$	−2.279	−0.750	−0.141	0.060
6491	$-\infty$	−1.331	−0.581	−0.227	−0.053
6576	0.514	0.328	0.175	0.070	0.015
8001	$-\infty$	−2.201	−1.114	−0.553	−0.215
8002	$-\infty$	−0.888	−0.297	−0.084	−0.014
8005	−1.703	−0.325	−0.119	−0.037	−0.006
8006	$-\infty$	−0.224	−0.057	−0.009	0.000
8007	0.301	0.255	0.204	0.146	0.079
8008	0.899	0.722	0.539	0.356	0.175
8010	$-\infty$	−0.253	−0.092	−0.036	−0.010
6371	0.602	0.465	0.318	0.170	0.049
1000	0.292	0.208	0.129	0.062	0.016
1001	$-\infty$	−0.229	−0.060	−0.011	−0.001
1002	0.292	0.208	0.129	0.062	0.016
442	$-\infty$	−0.425	−0.161	−0.043	0.003
Total	$-\infty$	−4.996	0.088	1.328	1.044

HOMOG utilizes two parameters, α and θ, to define three hypotheses: α is defined as the proportion of families showing linkage and θ is the recombination fraction. The null hypothesis, H_0, is that there is no linkage; α is set at 0 and θ at 0.5 (random assortment). The first alternate hypothesis (H_1) is that all of the families show linkage to the marker; α is set at 1.0 and θ is estimated from the data. The second alternate hypothesis is that heterogeneity exists; both α and θ are estimated from the data.

The results of this analysis are shown in table VI. For the hypothesis of heterogeneity, α was estimated to be 20%. The null hypothesis of no linkage can be rejected when compared to either of the alternate hypotheses. In addition, when the hypothesis of heterogeneity is compared to the hypothesis of homogeneous linkage, the hypothesis of homogeneity is just barely rejected ($P = 0.044$).

If there is heterogeneity, in that some families are linked and others are not, it is clear that summing LOD scores over all families is not valid. This means that the traditional criteria for acceptance of linkage, a total LOD score greater than 3, is not obtainable unless some external criteria can be found to subdivide families, or if analysis is restricted to

Table VI. Test of Homogeneity (HOMOG; J. Ott): Reading Disability versus Chromosome 15 Heteromorphisms

H_0: No linkage ($\alpha = 0.00, \theta = 0.50$)
H_1: Linkage with homogeneity ($\alpha = 1.00, \theta = 0.30$)
H_2: Linkage with heterogeneity ($\alpha = 0.20, \theta = 0.00$)

	df	chi-square	*p*-value
H_2 vs. H_1	1	2.910	0.0440
H_1 vs. H_0	1	7.000	0.0041
H_2 vs. H_0	2	9.910	0.0035

very large families. Ott (1985) has suggested that, alternatively, the hypothesis of linkage may be accepted if the significance level for at least one of the three tests in HOMOG is significant at least at the 0.001 level. The results shown in table VI do not reach this criterion, since the *P* value for the most significant test (H_2 versus H_0) is 0.003.

Multipoint Analysis

The results of the multipoint analysis are shown in table VII. In addition to the chromosomal heteromorphisms, data from two DNA markers, TH114 and DP151, are included. These markers were the most informative and closest to the heteromorphisms of the DNA markers tested. The addition of DNA markers in a multipoint analysis of linkage supports, but does not add to, the overall LOD score or to the LOD score for Family 6432. When the test for homogeneity is performed with these data, the null hypothesis of no linkage cannot be rejected when compared to the hypothesis of linkage with homogeneity, but both the null hypothesis and the hypothesis of homogeneity are rejected when compared to the hypothesis of heterogeneity (table VIII). Again, however, the significance levels are not great enough to establish linkage without other confirming evidence. Thus, the results of both the two-way and multipoint linkage analyses do not confirm the existence of linkage, but do suggest that, if linkage exists, there is heterogeneity with only about 20% of the families showing linkage to chromosome 15.

Linkage results with markers from chromosome 6 were quite similar, but there were some interesting findings when these results were contrasted with the chromosome 15 data on a family-by-family basis. Again, the total LOD scores were not high (table IX); however, several families had LOD scores greater than 1.0, and Family 6432, which showed strong evidence for linkage to chromosome 15, shows negative linkage to chromosome 6 markers. In fact, families that tended to show stronger linkage to one chromosome tended to show less linkage to the

Table VII. Multipoint Linkage between SRD and Chromosome 15 Markers

	Markers and Map Position													
	0.4	**0.3**	**0.2**	**0.1**	**15 centromere**		**0.075**	**0.15**	**0.225**	**TH114**		**0.03**	**0.07**	**DP151**
Family														
9007	0.019	0.027	−0.056	−0.395	−17.917	−∞	−0.485	−0.081	0.054	−0.033	−0.033	−0.127	−0.337	−∞
9008	−0.001	−0.027	−0.079	−0.224	−15.599	−∞	−0.296	−0.125	−0.095	−0.262	−0.262	−0.370	−0.584	−1.511
9102	−0.040	−0.169	−0.429	−0.964	−32.035	−∞	−1.223	−0.693	−0.461	−0.517	−0.517	−0.617	−0.840	−∞
6372	0.201	0.276	0.164	−0.350	−46.660	−∞	−0.614	0.030	0.295	0.410	0.410	0.423	0.434	0.444
6375	0.220	0.431	0.625	0.780	0.831	0.831	0.851	0.812	0.730	−∞	−∞	−0.290	−0.568	−∞
6432	**0.712**	**1.316**	**1.857**	**2.361**	**2.838**	**2.838**	**2.427**	**1.984**	**1.457**	**−0.233**	**−0.233**	**0.821**	**0.826**	−∞
6484	0.058	−0.149	−0.769	−2.315	−∞	−∞	−3.084	−1.467	−0.853	−1.154	−1.154	−1.488	−2.184	−∞
6491	−0.053	−0.227	−0.581	−1.331	−47.864	−∞	−1.727	−1.030	−0.813	−1.155	−1.155	−1.403	−1.896	−∞
6576	0.015	0.070	0.175	0.328	0.514	0.514	0.372	0.247	0.144	0.070	0.070	0.060	0.051	0.042
8001	−0.214	−0.549	−1.107	−2.190	−49.853	−∞	−2.651	−1.519	−0.886	−0.450	−0.450	−0.382	−0.316	−0.250
8002	−0.014	−0.084	−0.297	−0.888	−47.239	−∞	−1.155	−0.469	−0.183	−0.115	−0.115	−0.130	−0.160	−0.211
8005	−0.006	−0.037	−0.119	−0.325	− 1.703	−1.703	−0.424	−0.197	−0.091	−0.037	−0.037	−0.031	−0.025	−0.020
8006	0.000	−0.009	−0.057	−0.224	−15.647	−∞	−0.422	−0.256	−0.255	−0.480	−0.480	−0.603	−0.834	−1.808
8007	0.059	0.098	0.120	0.127	0.118	0.118	0.028	−0.107	−0.347	−1.011	−1.011	−1.312	−1.862	−∞
8008	0.175	0.356	0.539	0.722	0.899	0.899	0.747	0.576	0.361	−0.041	−0.041	−0.198	−0.476	−∞
8009	−0.002	−0.007	−0.016	−0.029	− 0.047	−0.047	−0.066	−0.102	−0.179	−0.444	−0.444	−0.576	−0.830	−∞
8010	−0.010	−0.035	−0.091	−0.252	−15.654	−∞	−0.333	−0.132	−0.038	0.038	0.038	0.054	0.071	0.091
381	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
442	0.002	0.004	0.005	0.006	0.006	0.006	0.006	0.006	0.003	−0.004	−0.004	−0.007	−0.012	−0.018
Total	1.121	1.285	−0.116	−5.163	−∞	−∞	−8.049	−2.523	−1.157	−∞	−∞	−6.176	−9.542	−∞

Table VIII. Test of Homogeneity (HOMOG; J. Ott): Reading Disability versus Three Chromosome 15 Markers

H_0: No linkage ($\alpha = 0.00, \theta = 0.50$)
H_1: Linkage with homogeneity ($\alpha = 1.00, \theta = 0.50$)
H_2: Linkage with heterogeneity ($\alpha = 0.20, \theta = 0.00$)

	df	chi-square	*p*-value
H_2 vs. H_1	1	9.070	0.0013
H_1 vs. H_0	1	0.000	0.5000
H_2 vs. H_0	2	9.070	0.0054

other. This is shown graphically in figure 2, in which the LOD scores for each chromosome at $\theta = 0.1$ are compared for each family, with the families arranged in descending order of the LOD score for chromosome 15.

When the HOMOG analysis was performed with these data from the chromosome 6 markers, α was again estimated to be 20% (table X). The null hypothesis of no linkage was rejected compared to both alternate hypotheses, and the hypothesis of heterogeneity was preferred, but significance levels were not high enough to declare linkage based on these data alone.

In an effort to determine if some of the heterogeneity was contributed by Family 6432, HOMOG was re-run with this family omitted (table XI). The estimate of α increased to 0.85 families linked, and the null hypothesis of no linkage was again rejected, but now the hypothesis of homogeneity could not be rejected when compared to the hypothesis of heterogeneity. Thus, it appears that Family 6432, selected solely on the basis of the linkage results with chromosome 15, contributed to the heterogeneity of linkage seen with chromosome 6, and its omission increased the probability that the remaining families were all linked to chromosome 6. Finally, the significance level reached for linkage with homogeneity would meet Ott's (1985) suggested criteria for acceptance of linkage.

A linkage map showing the results of linkage to chromosome 6 with and without Family 6432 reflects slightly higher total LOD scores, with the highest probability of linkage in the GLO region (figure 3).

Future Studies

Based upon the results of the present study, it can be hypothesized that some families show linkage of reading disability to chromosome 15 but not chromosome 6, and others (a greater proportion) show linkage to chromosome 6 but not 15. In addition to continued studies to increase the number of large families and the number of informative markers for

Table IX. Multipoint Linkage between SRD and Chromosome 6 Markers BF, GLO, and 2C5

Marker	Map Position											
					Bf		2C5	GLO				
	0.1	0.2	0.3	0.4	0.5	0.55	0.58	0.60	0.70	0.80	0.90	1.00
Family												
9007	0.048	0.011	−0.178	−0.750	−∞	− 1.366	−0.899	−0.694	−0.193	0.003	0.062	0.051
9008	0.129	0.190	0.146	−0.098	−∞	− 1.426	−1.487	−1.111	−0.084	0.178	0.222	0.149
9102	0.155	0.487	0.848	1.195	1.519	1.640	1.706	1.749	1.389	0.993	0.570	0.177
381	0.030	0.351	0.748	1.133	1.494	1.474	1.472	1.475	1.109	0.721	0.333	0.045
442	0.061	0.135	0.172	0.060	−∞	− 1.141	−1.662	−∞	−0.160	0.102	0.123	0.062
6372	0.071	0.163	0.205	0.132	−0.176	− 0.660	−1.371	−∞	−0.160	0.159	0.183	0.086
6375	−0.266	−0.567	−0.980	−1.742	−∞	− 5.299	−∞	−2.894	−1.281	−0.763	−0.463	−0.229
6432	**−0.182**	**−0.456**	**−0.949**	**−1.963**	−∞	**− 3.991**	**−4.550**	−∞	**−2.776**	**−1.426**	**−0.695**	**−0.249**
6484	0.136	0.154	−0.017	−0.552	−2.248	− 4.118	−∞	−2.712	−0.164	0.374	0.434	0.264
6491	0.068	0.245	0.477	0.724	0.964	0.967	0.973	0.978	0.740	0.493	0.257	0.072
6576	−0.078	−0.187	−0.362	−0.690	−1.891	− 1.186	−1.392	−∞	−0.605	−0.333	−0.191	−0.090
8001	0.098	0.153	0.125	−0.090	−∞	− 2.269	−∞	−∞	−0.483	−0.120	0.008	0.033
8002	−0.001	−0.012	−0.045	−0.114	−0.231	− 0.351	−0.415	−0.454	−0.280	−0.128	−0.043	−0.007
8005	−0.002	−0.003	0.004	0.027	0.069	0.104	0.128	0.146	0.067	0.019	−0.001	−0.003
8006	−0.018	−0.076	−0.194	−0.444	−∞	− 0.695	−0.531	−0.456	−0.234	−0.116	−0.048	−0.011
8007	0.032	0.056	0.070	0.047	−0.099	− 0.425	−∞	−0.543	0.011	0.074	0.062	0.035
8008	−0.017	−0.074	−0.189	−0.429	−1.703	− 1.377	−1.475	−1.703	−0.429	−0.189	−0.074	−0.017
8009	0.028	0.463	0.726	0.976	1.204	1.184	1.180	1.180	0.954	0.707	0.448	0.199
8010	−0.004	−0.018	−0.042	−0.078	−0.129	− 0.169	−0.197	−0.204	−0.119	−0.063	−0.027	−0.007
Total	0.468	1.015	0.565	−2.656	−∞	−19.104	−∞	−∞	−2.698	0.685	1.160	0.560

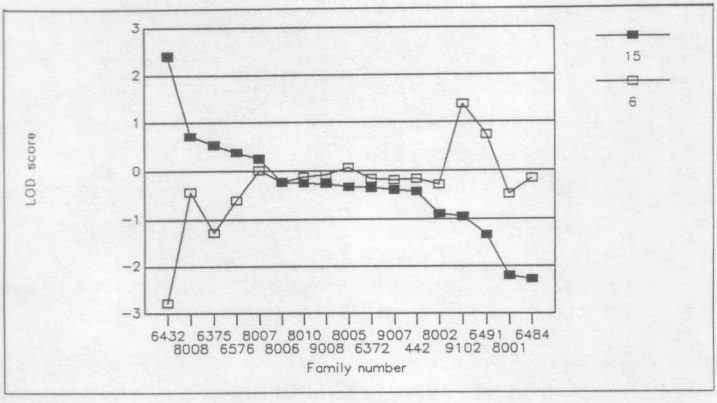

Figure 2. Comparison of LOD scores for markers on chromosomes 6 and 15. The families are listed along the x-axis in descending order of their LOD scores for chromosome 15 heteromorphisms at 10% recombination. These scores are indicated by the closed circles. The LOD scores for the chromosome 6 markers at 10% recombination for each family are shown by the open squares.

these two regions, two other approaches to gene localization will be utilized, namely the affected sib-pair method (Blackwelder and Elston 1985) and the method of interval mapping for quantitative trait loci (Lander and Botstein 1989).

The sib-pair method is based on the assumption that, if a major gene for a trait is tightly linked to a marker gene, a pair of sibs who are both affected with the trait will also tend to be concordant for the same linked allele. A significant discrepancy from random assortment of the trait and the marker allele can be taken as evidence for linkage. This is not as powerful as the family study method, and is generally used as a screen for candidate loci for more intensive family studies, but it also has some advantages over the family study method that are particularly appropriate for the study of reading disability. The primary advantages are that it can be used to test for a locus conferring a non-Mendelian susceptibility for a trait and that assumptions about the

Table X. Test of Homogeneity (HOMOG; J. Ott): Reading Disability versus Chromosome 6 Markers

H_0: No linkage ($\alpha = 0.00, \theta = 0.50$)
H_1: Linkage with homogeneity ($\alpha = 1.00, \theta = 0.30$)
H_2: Linkage with heterogeneity ($\alpha = 0.20, \theta = 0.00$)

	df	chi-square	*p*-value
H_2 vs. H_1	1	2.947	0.0430
H_1 vs. H_0	1	5.342	0.0104
H_2 vs. H_0	2	8.289	0.0079

Table XI. Test of Homogeneity (HOMOG; J. Ott): Reading Disability versus Chromosome 6 Markers, Family 6432 Omitted

H_0: No linkage ($\alpha = 0.00, \theta = 0.50$)
H_1: Linkage with homogeneity ($\alpha = 1.00, \theta = 0.20$)
H_2: Linkage with heterogeneity ($\alpha = 0.85, \theta = 0.20$)

	df	chi-square	*p*-value
H_2 vs. H_1	1	0.364	0.2731
H_1 vs. H_0	1	9.722	0.0009
H_2 vs. H_0	2	10.086	0.0032

mode of inheritance or penetrance of the trait do not need to be made. In addition, other family members do not need to be diagnosed, which alleviates the problem of compensation. However, the markers must be highly polymorphic so that alleles that are shared can be assumed to be identical by descent. Preliminary computations with informative sib pairs in our families show that neither chromosome 15 heteromorphisms nor GLO types show significant sharing; however, only 9 sibships (25 sib pairs) could be unambiguously scored for chromosome 15, and only 14 sibships (37 pairs) could be scored for number of shared GLO alleles (0–1 versus 1–2). Clearly, these single loci are not polymorphic enough for this analysis, and multiple loci must be used.

The methods for searching for quantitative trait loci (Lander and Botstein 1989) will also be very useful in identifying chromosomal regions for further analysis. Since multiple chromosomal regions can be

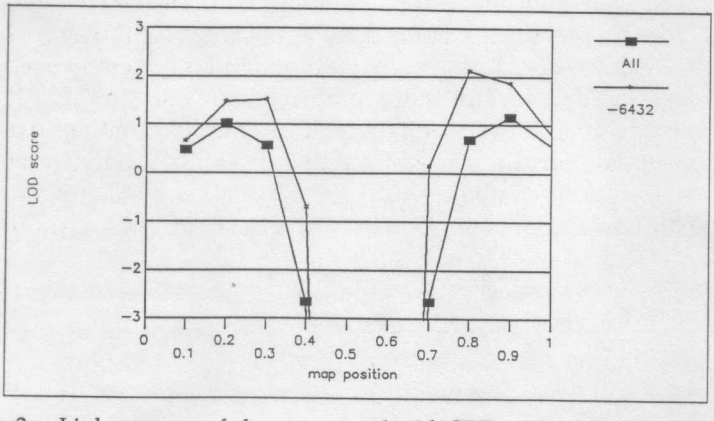

Figure 3. Linkage map of chromosome 6 with SRD with and without Family 6432. The x-axis represents the relative genetic position of the markers (in recombination units) along the long arm of the chromosome. The multipoint LOD scores for the total population studied are shown by the closed circles. As indicated by the open boxes, the LOD scores for chromosome 6 markers increase when the scores from Family 6432 are subtracted from the total.

considered simultaneously, it may be possible to begin to assess the extent to which reading deficits are due to individual quantitative trait loci.

CONCLUDING REMARKS

During the past five years, several important results have been obtained by co-investigators associated with the Colorado Reading Project. Within the Twin/Family Study component, a new multiple regression analysis of twin data has been developed that provides compelling evidence for a genetic etiology of reading disability. In addition to being statistically powerful, this methodology is highly flexible and is presently being used by Colorado Reading Project investigators to test various hypotheses that are relevant to important issues in the field of learning disabilities. For example, we are currently employing the multiple regression analysis of twin data to validate alternative typologies and evaluate the assumption of specificity (Foorman 1989; Stanovich 1986).

Within the Reading and Language Processes component, investigators have found that disabled readers have phonological coding skills that are well below the levels expected on the basis of their word recognition skills, whereas their performance on an orthographic task is slightly better than expected. Moreover, employing a bivariate form of the multiple regression analysis of twin data, evidence has been obtained to indicate that the correlation between phonological coding and word recognition is largely due to heritable influences, whereas the relationship between orthographic coding and word recognition is due primarily to environmental influences.

Within the Epidemiology of Immunological Differences component, no association has been found between reading disability and prevalence of immune disorders. However, comparisons of MZ and DZ concordance rates suggested the possible validity of a genetic subtype of reading disability with atopic disorders, a result which is convergent with the preliminary evidence for linkage between reading disability and chromosome 6 found in the Linkage Analysis component.

Results obtained by co-investigators within the Linkage Analysis component strongly suggest that reading disability is etiologically heterogeneous. For example, the co-investigators have found that about 20% of families with apparent autosomal dominant transmission for reading disability manifest linkage to chromosome 15, but not to chromosome 6. Some evidence for linkage to chromosome 6, but not to 15, was obtained from data on other families. The co-investigators are currently increasing their sample size and the number of informative markers on chromosomes 15 and 6, and are beginning to employ the

method of interval mapping to search for quantitative trait loci that may influence reading disability.

In addition to these within-component analyses, several cross-component analyses are also currently in progress. For example, using state-of-the-art segregation analysis computer programs, currently we are conducting a genetic analysis of data from over 400 families that have been ascertained within the various components. Another example is a linkage analysis of data from fraternal twins in which our multiple regression analyses of twin data will be used to assess the extent to which the reading performance deficit of probands is due to quantitative trait loci. In this manner, the methods of quantitative genetics, developmental psychology, clinical psychology, and medical genetics are being combined to obtain a more complete understanding of the etiology of reading disability.

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