Evidence for Major Gene Transmission of Developmental Dyslexia

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Objective.—There is strong evidence that developmental dyslexia is both familial and heritable, but the mode of genetic transmission has remained unclear. In this article, we examine specific genetic hypotheses about the mode of transmission of developmental dyslexia by performing complex segregation analyses.

Design.—A family study method was applied, whereby the relatives of dyslexic probands were examined for dyslexia. The families studied represent four independently ascertained samples.

Setting.—The four samples of families were primarily from rural and suburban communities of Colorado, Washington State, and Iowa.

Participants.—A total of 204 families and 1698 individuals in the four samples combined.

Main Outcome Measures.—The complex segregation program, POINTER, was used to test competing genetic hypotheses of how a categorical trait (dyslexia) is transmitted in families.

Results.—The results were consistent with major locus transmission in three of four samples and with polygenic transmission in the fourth. In these three samples, the estimates of penetrance for the Aa, Aa, and aa genotypes (where A is the abnormal allele) were, respectively, 1.000, 1.000, and 0.001 to 0.039 in males, and 0.560 to 1.000, 0.550 to 0.897, and 0.000 in females. The estimated gene frequency of the major locus was between 3% and 5%.

Conclusions.—Sex-influenced, additive, or dominant transmission occurs in a significant proportion of dyslexic families. Other evidence indicates, however, that dyslexia is etiologically heterogeneous and that there is genetic heterogeneity even among families selected for apparent dominant transmission. Thus, while no single major locus may account for all of dyslexia, it is important to pursue potential major loci for dyslexia using linkage techniques.

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CLINICIANS have known for a long time that dyslexia appears to run in families. Soon after development of dyslexia was first described in 1896 by Kerr and Morgan, several reports of familial aggregation appeared, one of which reported a kindred with three affected generations. However, compelling evidence that dyslexia is both familial and heritable has only emerged recently, and the mode of transmission has remained unclear. The genetic influences on dyslexia could be polygenic, with dyslexia being just the lower tail of a multifactorially determined normal distribution of reading skill. Alternatively, only one or a few major genes could underlie much of what we call dyslexia. These possibilities are not mutually exclusive, since major genes could operate in the context of a multifactorial background—the so-called mixed model, which may be more appropriate for understanding the genetics of complex behavioral disorders such as dyslexia. Whether there is major gene transmission in complex behavioral disorders is a fundamental issue that goes to the heart of how we conceptualize and treat such disorders. Modern segregation and linkage techniques can resolve this issue. This report presents the largest and most comprehensive segregation analysis of dyslexia to date; the results have important implications for the application of genetic linkage techniques to this common disorder.

Few studies have actually examined the mode of transmission of dyslexia. In 1950, Hallgren studied 112 families, each identified through a child with dyslexia, and found support for autosomal dominant transmission with a possible sex difference in penetrance. However, his study has been criticized because it did not use objective tests to diagnose siblings and parents or consider the possibility of genetic heterogeneity. The only study to date that used formal segregation analysis is the Colorado Family Reading Study (CFRS), in which all numbers were formally tested. Contrary to Hallgren's results, there was no evidence for major locus transmission of
dyslexia in the CFRS sample taken as a whole. However, when the sample was subdivided, this study found evidence favoring autosomal recessive transmission in the families of female probands and additive transmission when the children were analyzed alone; these subsample differences suggested genetic heterogeneity. A continuous discriminant score was the CFRS phenotype, and the data were analyzed by the segregation package GENSEG.

Possible shortcomings of the CFRS study are that it did not make any provision for the phenomenon of compensation in adults and that it was unable to test the mixed model. Since approximately one fifth of children with dyslexia test normal as adults, 47 not allowing for compensation in the adult phenotype may bias a segregation analysis against finding a major locus effect. Testing the mixed model is important because complex behavioral disorders such as dyslexia may have both major locus and multifactorial effects on their transmission.

At approximately the same time the CFRS was being conducted, another group of investigators began pursuing Hallgren's hypothesis of dominant transmission by conducting linkage analyses in three-generation dyslexic families with apparent autosomal dominant transmission. In 1983, they reported evidence for linkage between dyslexia and centromeric heteromorphisms on chromosome 15 in nine extended families. 69 Subsequently, 12 more extended families have been studied, along with additional branches of some of the original families. In this larger sample, there is statistically significant evidence of genetic heterogeneity and continuing evidence for a locus on chromosome 15. These findings should be interpreted in light of a separate study that failed to find evidence for linkage between dyslexia and chromosome 15 heteromorphisms in five nuclear families whose diagnoses were determined by questionnaire. 74 Thus, confirmation of the chromosome 15 results requires further study.

In summary, the possibility of autosomal dominant transmission in dyslexia remains an intriguing, elusive, and controversial possibility. 6,10 Such a mode of transmission would provide a parsimonious explanation for the consistently high familial recurrence rates reported for this disorder (35% to 45%), which are several times higher than the estimated population base rates of 3% to 10%. 74 In our present study, we examined the transmission patterns of dyslexia in four samples of families, including the CFRS and Linkage samples. In two samples, we were able to use a phenotype that provided for compensation in adults. The statistical package POINT-ER, 19 which tests the mixed model, was used, and variations across studies in ascertainment and phenotype definition provided a test of the robustness of any converging results obtained.

METHODS

Colorado Nuclear Families

Subjects.—All subjects were tested as part of the CFRS at the Institute for Behavioral Genetics, Denver, Colo, between 1973 and 1976. Probands that met the following four criteria were referred to us by school personnel: (1) age from 7.5 through 12. (2) reading level equal to or less than half the expected grade level (eg, a child in fourth grade reading at or below the second-grade level), (3) an IQ of at least 90 on any of the standardized tests administered by the school, and (4) residence with both biological parents.

All family members were tested by trained examiners at the Institute for Behavioral Genetics. Relevant tests for the current analyses include the Peabody Individual Achievement Test (PIAT) 20 and the Institute for Personality and Ability Testing Nonverbal Culture Fair Intelligence Test (IPAT). 21 Information about reading history was collected on parents and probands (who, by definition, had a history of reading problems) but not on siblings.

Diagnosis of Reading Disability.—A subject was classified as reading disabled if he or she had either a history of reading problems or a significant discrepancy between ability and reading and spelling achievement on the PIAT as measured by the specific dyslexia algorithm. 10 This definition includes compensated adults (those with a history, but a normal specific dyslexia algorithm). The Specific Dyslexia Algorithm subtracts the lower of PIAT reading recognition or spelling standard scores from the higher of PIAT mathematics standard score or IPAT IQ score. If this difference score is 15 points (1 SD) or greater, the discrepancy is considered significant. If neither PIAT reading recognition nor spelling standard scores are below the population mean (≤1 SD), then the required discrepancy is 30 points. In this and the other three samples, the usual exclusionary criteria were also applied (ie, no peripheral visual or auditory impairment, no known neurological damage, and no severe psychiatric problems).

The Linkage Kindreds

Subjects.—As part of a collaborative linkage study, 5,16 three-generation kindreds selected through a dyslexic proband have been identified, and data on approximately 268 biological relatives have been obtained. All probands were ascertained through clinics or parent groups or children who were reading disabled, and only those pedigrees suggestive of autosomal dominant transmission of dyslexia were included. Obviously, this selection procedure biases the results of a segregation analysis; the Linkage sample is included herein only for comparison purposes.

Both the occupational status 22 (mean, 2.68 on a seven-point scale) and the educational level (mean years of schooling, 14.75) of the adults in these families are above average. Consenting family members were tested and interviewed by trained personnel. Among the cognitive tests were Raven's Progressive Matrices, 23-25 PIAT, 26 portions of the Wide Range Achievement Test, 27 and the Gray Oral Reading Tests. 28

Diagnosis of Reading Disability.—The same phenotype definition was used as that in the main CFRS analysis: history or specific dyslexia algorithm.

The Washington Kindreds

Subjects.—Potential affected probands were drawn from a pool of all students in the middle school of a small western Washington town. Potential probands had been previously diagnosed as reading disabled by the school between 1975 and 1988. Probands had been tested by the researcher (S.A.S.) conducting the Washington study while she was a special education teacher in the Washington school district. Of the 185 individuals in the pool, 132 were 18 years or older at the start of the study and tested in the desired age range. Fifty of these persons were successfully reached by telephone.

In order to test families of sufficient size to examine transmission patterns over several generations, the 27 persons with at least 10 family members living within a 160-km radius of the experimenter were asked to participate. Twelve declined, two had complicating drug and alcohol abuse themselves and in their families, and three were later unable to complete the testing because of family emergencies. The remaining nine probands were of northern European and French ancestry. A total of 156 persons (first-, second-, and third-degree relatives) were tested and/or interviewed. No significant differences in the sex ratio or occupational level of the reading disabled were found between the families choosing to participate and those declining. Most adult participants were skilled or semiskilled craftspeople or laborers. However, considerably
more of the participating probands (69%) reported other relatives "who had learning problems in school," while 35% of those with fewer than 10 nearby relatives knew of other affected family members, possibly reflecting smaller overall family size.

A large battery of tests and a two-part questionnaire were administered to adults. Among the cognitive tests were PIAT, portions of the Wide Range Achievement Test, the Gray Oral Reading Tests, and Raven’s Progressive Matrices. In the nine proband families, testing, interview, and survey information could be obtained for 156 persons.

Diagnosis of Reading Disability.—

The method of diagnosis was similar to that used in the previous two studies but more conservative because only untested adults (n = 14) could be given a diagnosis by history alone, which had to include convergent self-reports as well as other reports. To be classified as reading disabled, a tested subject was required to have at least one subtest from the PIAT or the Wide Range Achievement Test batteries that was at least one SD below age or grade expectations, in addition to at least one other indicator of reading disability: a history of dyslexia or another pattern on objective test data that indicated that a subject was performing significantly below expectation (eg, the specific dyslexia algorithm). The overall agreement rate between this phenotype definition and that used in the previous two samples was approximately 79%.

The Iowa Kindreds

Subjects.—Forty extended families were identified through dyslexic probands seen at the University of Iowa Pediatric Psychology Clinic in Iowa City (Jeffrey W. Gilger, PhD, unpublished data, August 1989). These probands met the inclusionary and exclusionary criteria detailed in Diagnostic and Statistical Manual of Mental Disorders, Third Edition and demonstrated the “memory deficit” subtype of the University of Iowa diagnostic scheme. This subtype is defined by selective deficits in verbal short-term memory, in the context of normal overall IQ, with no significant discrepancy between verbal and performance IQ. It is the most common and most familial reading disability subtype seen in this clinic. Data on 50 potential control families, selected through an unaffected proband matched to the dyslexic index case on IQ, socioeconomic status, age, and sex were also obtained.

The 40 affected families were obtained from 86 potential families contacted. Sixty-two (63%) of these 86 originally agreed to take part, but 18 later dropped out. Most of the adult relatives were high school-educated and employed in jobs related to farming and agriculture. Specifically, on the 10-point scale of occupational status developed by Reiss, in which scores range from 1 (unskilled) to 10 (professional), parents of affected probands obtained a mean of 5.2.

Archival objective test data (national and state percentile scores) from the Iowa Tests of Basic Skills (ITBS) were obtained for the probands and their siblings, cousins, aunts, uncles, and parents. The ITBS batteries assess a wide variety of academic areas, are well standardized, and appear to be reliable and valid instruments. Until now, test, interview, and survey data have been collected on 669 blood relatives in affected kindreds. An attempt was made to collect at least one set of scores representing the elementary school years (third through eighth grades) and at least one set from the high school years (ninth through 12th grades) of all subjects. A success rate of approximately 85% has been achieved in searches for scores for individuals tested before 1978. For a majority of these subjects, multiple school years have been retrieved. The probands’ grandparents, because of their age, had no test data available.

Diagnosis of Reading Disability.—

The phenotype in this sample differed from the previous three because it relied on group rather than individual tests; unlike the first two samples, it did not consider compensation. Nonproband subjects were classified through an algorithm using the survey and test data. The definition of reading disability varied, depending on the generation of the subject and the data available. For grandparents only, self-reported historical information was used: reading disability was defined as having ever been in special education, finding learning very difficult in the school years, and indicating poor achievement in the first through third, fourth through eighth, or ninth through 12th grades. The diagnoses of all other relatives were determined by ITBS test scores alone or by ITBS scores and history. The first criterion required a significant discrepancy between reading-related ITBS scores and performance expectancies based on ITBS subtests less reliant on reading-related abilities. Specifically, subjects were identified as reading disabled if their work or mathematics ITBS composites were greater than the 98th percentile, while their reading, vocabulary, or language composites were less than the 26th percentile. Next, a history plus achievement deficit method was used when a subject was diagnosed as having a reading disability if he or she had reading, language, or vocabulary composites lower than the 26th percentile and reported a history of difficulty in learning. The choice of percentile cutoffs (ie, below the 26th or above the 86th percentile) was determined by those cutoffs best discriminating the reading-disabled and control probands.

Preliminary Analyses

Tables 1 and 2 provide further information about the four samples we submitted to segregation analysis. As can be seen, 204 families, with a total of 1698 individuals, were analyzed. The male-to-female ratio of affected individuals (excluding probands) ranged from 1.2:1 to 1.7:1, which is characteristic of family samples. These ratios are lower than the commonly cited sex ratio of approximately 4:1, but slightly higher than the recently reported equal sex ratio in a young, epidemiologic sample. The risk to primary relatives of probands is generally in the range found in other studies. In the three samples with extended families, the proportions of affected non-first-degree relatives of probands were 46%, 64%, and 21%, respectively, for the Linkage, Washington, and Iowa samples. These figures indicate considerable familial aggregation of this trait. The compensation rate of 22% is the same in both the CFRS and Linkage samples, indicating that approximately one fifth of adults who potentially have the genotype for dyslexia would be missed by a phenotype definition based on test scores alone. (Two thirds of the extended families in the Linkage sam-
ple had at least one compensated adult; compensated individuals were evenly distributed across these families, and compensation did not appear to define a subtype of families. Because only nuclear families were studied in the CFRS sample, it was not feasible to look for clustering of compensated individuals in that sample. The Washington and Iowa phenotypes precluded an examination of compensation rates in those samples.

In Table 2, it can be seen that the reading-disabled and non-reading-disabled relatives were generally similar in mean age and IQ but differed substantially in reading achievement. In all samples except the Iowa sample, the difference between the two groups in reading scores is greater than the difference, if any, in mathematics scores. These results follow from the differing phenotype definitions used and indicate that the Iowa phenotype definition was less specific than that used in the other three samples. This phenotype difference may help explain the different segregation analysis results found in the Iowa sample.

**SEGREGATION ANALYSES**

Segregation analyses were performed using the computer program **POINTER** 2.0, which allows for the specification of various genetic and population parameters. Family members with missing data were classified as "unknown" for these analyses. Each genetic model is defined by a set of four parameters: dominance, gene frequency, displacement or threshold, and "heritability" of the multifactorial-polygenetic background, which includes both transmissible polygenic and cultural influences. The dominance parameter, \((r_{D}, 0 \rightarrow 1)\) estimates the degree of dominance of a detected major locus; a value of 0 indicates a recessive effect, and a value of 1 indicates complete dominance. Gene frequency estimates the population prevalence of a detected major locus, given the population prevalence of the phenotype. Threshold estimates the degree of separation (in SD units) between the means of the distribution for the homozygous normal (aa) and homozygous abnormal (AA) genotypes. If the threshold equals zero, then there is no major locus effect and, thus, only one multifactorially determined distribution. The strength of the multifactorial effect (either with or without an accompanying major gene effect) is estimated by heritability \((r_{H}, 0 \rightarrow 1)\).

To test the robustness of our results, we conducted analyses using a range of parameter values. Analyses were run using population prevalences of 1.5%, 7.5%, and 10.0%; male-to-female ratios for dyslexia of 1:81 and 3:5:1; and a variety of values for the ascertainment probabilities. The ascertainment probability \((r_{A}, 0 \rightarrow 1)\) is an estimate of the likelihood of finding families similar to those in the sample, given some population of potential reading-disabled probands. Thus, low values represent rare families. Specifically, for the CFRS, ascertainment probabilities were .01, .50, and .90; for the Linkage and Iowa samples, .01 and .50; and for the Washington sample, .50 and .90. These parameter values were all in accordance with previous research and also bounded values empirically derived from our samples.

The **POINTER** analysis tests null hypotheses in order of increasing specificity. The first and broadest question is whether we can reject vertical transmission of the trait. If not, the next two more specific (and independent) questions are whether we can reject a mendelian (major locus) effect and whether we can reject a multifactorial effect. If we can reject neither, then it is concluded that a mixed model of transmission best fits the data. If a mendelian effect is found, the next (and most specific) questions are whether we can reject a particular major locus model: recessive, additive, or dominant.

Two important tests of the reliability, validity, and generalizability of our primary segregation analyses were also conducted. First, it is common practice when a major locus is detected to test the transmission probability of the heterozygote \((\text{tau}2)\). If allowing \(\text{tau}2\) to vary freely leads to a better fitting model than when it is constrained at its expected value of .50, then the general segregation results indicating major gene transmission are suspect. Second, goodness-of-fit \(x^2\) tests were performed to determine how well the observed rates of reading disability in our samples of families agreed with expected rates, which were determined by using the **POINTER** estimates of gene fre-
frequency and penetrance for each sample. In these analyses, significant \( \chi^2 \) statistics indicate that a particular POINTER solution (e.g., autosomal dominant) does not adequately predict the rates of reading disability observed in first-degree relatives.

RESULTS

Table 3 presents a summary of the POINTER results. The results of the multiple runs across the range of parameter estimates (e.g., ascertainment probabilities and prevalence) were generally convergent within samples. Therefore, we will describe in detail the results from the most representative set of analyses, where the population prevalence was set at 7.5%, the male-to-female ratio was set at 1.8:1, and the ascertainment probability was based on our best estimate of what was appropriate for each sample: 0.50 for the CFRS; 0.50 for the Washington sample; 0.01 for the Linkage study; and 0.01 for the Iowa families.

As can be seen in Table 3, vertical transmission was present in all four samples. There was also evidence of a major gene effect in three of the four samples. Evidence for a major gene effect was an important result, particularly for the CFRS sample, which was not biased toward a certain pattern of transmission, as were the Linkage and possibly the Washington samples. Only the Iowa data set failed to suggest a major gene effect. It was also the only sample for which heritability of the multifactorial-polygenic transmission could be detected.

Further examination of the data from the three samples that found a major gene effect revealed that the recessive models fit the data poorly. Both the additive (dominant, 0.50) and dominant (dominant, 1.0) gene models fit the data well, suggesting that the best solution to our data was major gene (dominant or additive) transmission with sex-dependent penetration.

Table 4 gives the parameter estimates of threshold and gene frequency for the dominant and additive models for the three samples that supported major gene transmission; the same estimates for the Iowa sample are given for comparison purposes. The similarity of these parameter estimates is noteworthy. The bottom dominance value (in parentheses) is the value obtained when the dominance parameter was allowed to vary. For the CFRS sample, this value approaches 1.0, or complete dominance, whereas in the Linkage and Washington samples, it is between 0.50 and 0.70, indicating incomplete dominance. While the Iowa data did not suggest major gene influence, the degree of heritability of the multifactorial-polygenic effects is high and estimated at 0.83.

Table 5 gives the estimates for the phenocopy rates (proportion affected, given the normal aa genotype) and sex-specific penetrances for the three samples that found a major gene effect. Again, these estimates are quite similar across samples. It is noteworthy that there are clear differences between the sexes for phenocopy rates and gene penetrance. A sex difference in the phenotypic expression of the gene was also suggested by the finding of gender-specific threshold values.

For the three samples that found a major gene effect, \( \chi^2 \) tests of goodness of fit between the predicted and observed rates of affected first-degree relatives (based on sex-dependent POINTER estimates shown in Tables 4 and 5) were performed. The resulting \( \chi^2 \) values, each with 5 df, for the dominant model were: 10.00 (\( P > .05 \)), 33.48 (\( P < .001 \)), and 31.53 (\( P < .001 \)) for the CFRS, Linkage, and Washington samples, respectively. For the additive model, the comparable statistics were: 8.80 (\( P > .05 \)), 31.79 (\( P < .001 \)), and 29.59 (\( P < .001 \)). Thus, it appears that the transmission of dyslexia in the CFRS sample is consistent with autosomal dominant or additive transmission, with sex-specific penetrance. (Chi-square tests were also performed using values derived from additive and dominant models with the male-to-female ratio set at 1:1, which constrained the sex-specific penetrances to be equal. This constraint led to the largest and most highly significant \( \chi^2 \) values, particularly for the CFRS sample. This result sug-

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Table 3. — Summary of Conclusions Drawn From Segregation Analyses

<table>
<thead>
<tr>
<th>Null Hypothesis</th>
<th>Colorado Family Reading Study</th>
<th>Washington</th>
<th>Linkage</th>
<th>Iowa</th>
</tr>
</thead>
<tbody>
<tr>
<td>No transmission</td>
<td>Rejected†</td>
<td>Rejected†</td>
<td>Rejected†</td>
<td>Rejected†</td>
</tr>
<tr>
<td>No major gene</td>
<td>Rejected†</td>
<td>Rejected†</td>
<td>Rejected†</td>
<td>Consistent†</td>
</tr>
<tr>
<td>No multifactorial/ polygenic effect</td>
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<td>Consistent†</td>
<td>Consistent†</td>
<td>Rejected†</td>
</tr>
<tr>
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<td>Rejected†</td>
<td>Rejected†</td>
<td>...</td>
</tr>
<tr>
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<td>Consistent†</td>
<td>Consistent†</td>
<td>...</td>
</tr>
<tr>
<td>No additive gene effect</td>
<td>Rejected†</td>
<td>Rejected†</td>
<td>Rejected†</td>
<td>...</td>
</tr>
</tbody>
</table>

*These results are based on a population prevalence of 7.5%, a male-to-female ratio of 1.8:1, and appropriate ascertainment corrections (see "Results" section of text).

†Null hypothesis rejected at \( P < .001 \).

‡Null hypothesis cannot be rejected at \( P < .05 \).

Table 4. — Dominant and Additive Model Parameter Estimates

<table>
<thead>
<tr>
<th>Study</th>
<th>Parameters</th>
<th>Gene Frequency</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorado Family Reading Study</td>
<td>Dominant</td>
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</tr>
<tr>
<td></td>
<td>Additive</td>
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<td>0.49</td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>[0.99]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Washington</td>
<td>Dominant</td>
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<td>0.30</td>
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<td>Additive</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>[0.50]</td>
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<td></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Linkage</td>
<td>Dominant</td>
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<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Additive</td>
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<tr>
<td></td>
<td>[0.50]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iowa†</td>
<td>Dominant</td>
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<td>0.06</td>
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<tr>
<td></td>
<td>Additive</td>
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<td>[1.00]</td>
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<tr>
<td></td>
<td>[0.50]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.99)</td>
<td></td>
<td></td>
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</tbody>
</table>

*The definition of the four parameters is explained in the "Segregation Analyses" section of the text. Dominance, gene frequency, and heritability can all range from 0 to 1. Threshold is expressed in SD units. Results are based on a population prevalence of 7.5%, a male-to-female ratio of 1.8:1, and appropriate ascertainment corrections (see "Segregation Analyses"). Values in brackets are set according to additive/dominant mendelian expectations. Values of dominance in parentheses are derived from general mendelian models, where dominance is allowed to vary.†For explanation of Iowa values, see "Segregation Analyses."

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gests that unequal sex ratios were appropriate for our data sets and that the sex difference in penetrance may not be purely artifactual.) Though similar genetic models were suggested for the Washington and Linkage samples, the significant \( \chi^2 \) values indicate that the additive or dominant models of transmission do not adequately fit the affection pattern observed in first-degree relatives. In almost every case, the observed number of first-degree relatives with reading disability exceeded POINTER predictions, particularly for males.

That a more complex genetic model may be appropriate for the Washington and Linkage samples is also suggested by the \( \tau_2 \) models we fit on the CFRS, Linkage, and Washington data sets. For all the genetic models presented thus far, the transmission probabilities for the three genotypes (AA, Aa, aa) of the susceptibility allele (\( \tau_1 \), \( \tau_2 \), and \( \tau_3 \)) were fixed at their mendelian values (1.0, 0.50, and 0). When major gene effects are suggested, it is common practice to fit at least one additional genetic model where dominance, threshold, gene frequency, heritability, and \( \tau_2 \) are allowed to vary simultaneously. Allowing \( \tau_2 \) to vary led to a significant improvement of fit in the Linkage and Washington data sets (\( P < 0.001 \)). The \( \tau_2 \) values for both samples bounded at 0.0062. For the CFRS sample, allowing \( \tau_2 \) to vary did not lead to a significant improvement of fit (\( P > 0.05 \)). (Allowing \( \tau_2 \) to vary did lead to a small but noticeable improvement of fit under the other two phenotype definitions examined in the CFRS sample.)

**COMMENT**

We reanalyzed the CFRS sample using a phenotype definition that included compensation in adults and a method of segregation analysis, POINTER, that incorporates the mixed model. Unlike the earlier results of Lewitter et al., we found that the best-fitting model was one incorporating a dominant or additive major gene effect. This result was robust over three different ascertainment probabilities (0.01, 0.50, and 0.99) and two different male-to-female ratios (3.5:1 and 1.8:1). Though the data are not shown in this article, we also found similar results using two other adult phenotype definitions (history alone as well as history and positive reading test findings) (B.F.P., J.W.G., D.P., S.A.S., S.D.S., J.C.D., unpublished data, January 1991). Thus, our results for the CFRS sample are not specific to a particular phenotype or to artifacts due to arbitrary parameter estimates. Instead, our results indicate that a major gene model best describes the transmission of dyslexia in these families, across a range of phenotype definitions. Given the high dominance estimate obtained from the general mendelian model (i.e., 0.99), a dominant gene effect seems to be operating in the CFRS families.

Because the much more restrictive phenotype of history and positive reading test results provided similar results, our results did not depend on including compensated adults. The remaining possible explanations for the differences between our results and those of Lewitter et al. include the use of (1) a categorical instead of a continuous phenotype, (2) IQ discrepancy in the definition of the phenotype, and (3) a different segregation analysis program. We are investigating the first two possibilities by repeating the segregation analysis of the CFRS sample with two different continuous phenotypes, one using IQ discrepancy and the other not. If the current results are robust in these new analyses, then the most likely explanation is the third one. Indeed, the segregation analysis programs, GENSEG and POINTER, do differ in several computational and parametric aspects.

The results in the Linkage sample were included here only for comparison purposes. We realized that the ascertainment procedures used for this sample violate some of the assumptions made by POINTER and that there is no way to correct for such a bias in a segregation analysis. The main importance of the Linkage sample is that it demonstrates the possibility and feasibility of identifying three- and sometimes four-generation kindreds with apparent major gene—particularly autosomal dominant—transmission of dyslexia. However, the existence of such kindreds, by itself, proves little, since they could occur by chance, representing the extreme tail of a distribution of kindreds in which the underlying mechanism of transmission was in fact polygenic or even cultural.

The Washington sample also demonstrated that it is not difficult to find kindreds with apparent major gene transmission of dyslexia. However, even though these families were not selected for a particular mode of transmission, they were selected on the basis of size (\( n = 10 \) or larger) and were a small subset of the original population cohort. As a result, families with multiple affected individuals may have been more likely to be identified, and once again, it is possible that there were an extreme group in which the apparent pattern of transmission occurred by chance. It is nonetheless important that the Washington sample produced similar results to those in the CFRS and Linkage samples, despite some differences in phenotype and large differences in demographic variables.

Thus, when considered separately, the results in the Linkage and Washington samples could simply be attributable to ascertainment bias. Moreover, this ascertainment bias is likely responsible for the deviations from expecta-
tion we discovered in the goodness-of-fit and tau$^2$ analyses for these two samples. However, when considered with the CFRS data, the converging pattern of results across all three samples argues strongly for major gene transmission in dyslexia. This transmission appears to be dominant or semidominant in a significant proportion of dyslexic families. Given the probable genetic heterogeneity among major gene forms of dyslexia, a"’s POYRNER’s estimates of gene frequency may be best interpreted as estimates of the combined prevalence of all major loci.

It is also noteworthy that for the additive model, the Aa and Ae penetrance were always equal (ie, 1.00) for males but not for females. This suggests that the heterozygote male may not be distinguishable from his homozygote counterpart. However, a single susceptibility allele is not as completely expressed in heterozygote females. Such a mechanism was previously postulated by Hallgren$^2$ and Sladen. $^9$ If there is indeed a sex difference in penetrance, it would help explain the sex differences commonly observed in the frequency and expression of reading disabilities, although these may not be as large as previously assumed.$^{27}$

In contrast to the other three samples, the Iowa results supported multifactorial-polygenic, rather than major locus transmission. It is unlikely that these results are due to the demographics of the sample, which were similar to the Iowa sample, or to the use of the "memory" subtype to select probands, since the majority of reading-disabled children in the clinic fell into this subtype, which also appears to be quite common in other samples of reading disability. Instead, a more likely explanation is the phenotype definition used for relatives. A much smaller proportion of the Iowa sample had test data, and only probands were tested individually. Because group tests, like the ITBS, are timed and require reading on all portions of the test, they more often confound reading skill with intellectual ability, making the differential diagnosis of specific reading disability vs low general ability quite difficult. Moreover, as noted earlier, only one of the three Iowa phenotypes required a discrepancy between reading and other academic skills. Thus, although the Iowa proband phenotype was quite specific, the definition used in relatives was broader than that used in the other samples and likely detected a wide range of individuals with academic difficulties, as the similar scores for reading and mathematics in the Iowa sample of reading disability (Table 2) suggest. Given this broader phenotype, it is not surprising that the Iowa results were different from those of the other three samples and appeared more multifactorial. Even so, when the Iowa sample was restricted to nuclear families of probands, for whom test data were more complete (J.W.G., unpublished data, January 1991), the pattern of results from POYRNER were much closer to that in the other three samples, although support for the major locus hypothesis only approached statistical significance, possibly because of power limitations.

There are several potential limitations to our results. First, it has been shown that under certain conditions, segregation analysis using the unified model can falsely support major locus transmission. A false-positive result can occur if the phenotypic distributions are skewed distal, borderline, or uncertain cases are included, or if only "loaded" pedigrees are selected. This last problem certainly applies to the Linkage study and possibly the Washington sample, but not to the CFRS sample. Although the main phenotype definition used (history or positive test results) is broad and possibly does detect mild, borderline, or uncertain cases, the results in the crucial CFRS sample were similar even when a much more restrictive phenotype definition was used.

Second, a valid concern is that our results almost certainly underestimate the effects of the environment, and probably the polygenic background, on dyslexia. The male penetrance estimates of 1.00 for both the homozygote and heterozygote seem high and are inconsistent with the male monozygotic twin concordance rate, which is substantially less than 1.00.$^{44}$ Simulation studies have, in fact, suggested that the unified model may underestimate the multifactorial background when the values of the dominance parameter are close to the pure mendelian case (0 for $ae$, and 1 for $aA$ and AA$^c$). Because the estimate of dominance for the CFRS (0.99) was close to the mendelian value of 1.0, the multifactorial background may have been underestimated.

In summary, we found support for probable dominant transmission of dyslexia in one of four samples (CFRS) and semidominant or additive transmission in two of the remaining three (Washington and Linkage). These results provide a parsimonious explanation for the consistently high familial risk rates (approximately 35% to 45%) found for dyslexia. They also encourage the continued use of genetic linkage techniques to confirm or disconfirm whether major loci are influencing dyslexia. Choosing appropriate parameter estimates for linkage analyses is difficult, particularly for complex disorders like dyslexia. Attempting linkage analyses with various "intuitive" parameter estimates, phenotypes, and assumed modes of transmission can lead to spurious conclusions and high rates of errors. It is therefore an appropriate strategy to conduct valid segregation analyses and apply the results to a later analysis for linkage. However, such a strategy will not circumvent the problem of genetic heterogeneity, which we have demonstrated in dyslexia$^2$ and which appears likely in many complex behavioral disorders. To deal with the problem of heterogeneity, three different strategies suggest themselves. Large single pedigrees can be studied separately, the joint probability of linkage to two (or more) independent loci can theoretically be computed in a sample of genetically heterogenous pedigrees, or sibling pair methods$^{45}$ can be used, which are less powerful but provide more robust results in a heterogeneous sample. Such studies are ongoing at the Learning Disability Research Center in Denver and Boulder, Colo.$^{46}$

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