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# Genetic Models of Reading Disability

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*Test data collected on 133 reading-disabled (RD) children and their nuclear families who participated in the Colorado Family Reading Study were subjected to segregation analysis utilizing the technique of Elston and Yelverton (1975) for a continuous phenotypic measure. The possibility of genetic heterogeneity of RD was investigated by analyzing four subsets of data: all families, families with male probands, families with female probands, and families with severely affected probands. Furthermore, an analysis of the children's data was compared to that of all family members to investigate the possibility that the disorder may be manifested differently in adults. Results from the four subsets of data show that RD is etiologically heterogeneous. Compatibility with a major recessive gene for RD was demonstrated for families with female probands. Analyses of the children's data alone give results consistent with both environmental and genetic determination of RD.*

**KEY WORDS:** dyslexia; reading disability; segregation analysis; family resemblance; genetic heterogeneity.

## INTRODUCTION

A learning disability may be defined as a handicap in speech, language, reading, writing, arithmetic, or other school subject not caused by mental

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retardation, sensory deprivation, or cultural or instructional factors (Kirk and Bateman, 1962). Although the concept of learning disability is relatively new, the specific form related to reading has been known for many years. The syndrome was first described in 1896 by Morgan and was termed "congenital word blindness." Various other terms for this disorder (including "dyslexia," "specific developmental dyslexia," and "specific reading disability") have subsequently been used. The term employed in the present article is "reading disability," abbreviated RD.

RD is of considerable concern to educators because of its frequency in school-age children. Although estimates have varied from less than 1% to more than 20% (Zerbin-Rüdin, 1967), typical estimates are usually in the range of 5–10% (McCarthy and McCarthy, 1969; Critchley, 1970). More males than females are usually found to be affected, with sex ratios of 3 or 4 to 1 being common.

Evidence for the familial nature of RD was first presented in 1905 by Thomas and by Fisher and in 1907 by Hinshelwood. Stephenson (1907) reported evidence of reading disability in three generations of a family. Additional evidence for the heritable basis of RD has since beeen obtained from both twin and family studies. Data from a total 113 twin pairs (48 identical and 65 fraternal) summarized to date by various investigators (Zerbin-Rüdin, 1967; Hallgren, 1950; Hermann and Norrie, 1958; Bakwin, 1973) indicated 90% concordance for identical twins vs. only 32% for fraternals.

The most extensive genetic analysis of RD previously reported is that by Hallgren (1950). In a sample of 112 families, Hallgren found that 88% of the probands had one or more affected relatives and concluded on the basis of various tests that the disorder followed an autosomal dominant mode of inheritance. However, 17% of the probands' families had both parents unaffected, a result entirely at variance with an autosomal dominant model. The diagnostic methods employed by Hallgren have been subject to some criticism (Owen, 1968), as have been the genetic analyses. For example, the methods used to estimate segregation frequencies (Weinberg's and Haldane's) fail to provide tests of internal consistency (Morton, 1958; Crow, 1965). In addition, in contrast to the finding of other investigators that RD is 3 or 4 times more frequent in males than in females, Hallgren (1950) observed little inequality in sex distribution among the affected relatives. Sladen (1970) has addressed this point and has hypothesized a sex-influenced model (dominant with incomplete penetrance in males, and recessive in females) to account for Hallgren's results.

Other genetic models for RD—including sex-linked recessive (Symmes and Rapoport, 1972), autosomal dominance with partial sex limitation (Zahalkova *et al.*, 1972), and autosomal dominance with polygenic

modifiers (Lenz, 1970)—have also been proposed. Finucci *et al.* (1976) have recently studied 20 children with RD and their nuclear families. Examination of the pedigrees provided evidence of familial aggregation of RD. It is improbable that it is due to familial environment, given that both very good and very poor readers occur within families. No single mode of genetic transmission was offered because inspection of the 20 pedigrees suggested that the disorder is genetically heterogeneous (i.e., various patterns of transmission were observed among the pedigrees).

None of the various models proposed for the inheritance of RD has been generally accepted. Lack of consensus regarding a particular mode of inheritance in previous studies of RD may be due to problems of small sample size, ascertainment, diagnosis, or genetic heterogeneity, as well as to a lack of powerful tests of specific hypotheses. The primary objective of the present study is to test various genetic models using data and methods less subject to these criticisms. The data consist of objective behavioral test scores obtained on 133 diagnosed RD children (probands), 125 of whom were matched with controls, and the nuclear families of all 258 children. The relatively large sample of probands was ascertained through local public schools and thus may lead to less bias than samples ascertained from clinic populations (Belmont and Birch, 1965). In addition, Elston and Yelverton's (1975) method of segregation analysis of quantitative traits was employed, which allows for both parameter estimation and hypothesis testing.

## MATERIALS AND METHODS

### Subjects

All subjects were tested as part of the Colorado Family Reading Study at the Institute for Behavioral Genetics between November 1973 and June 1976. Children with diagnosed reading problems were ascertained by referral from school psychologists, reading specialists, or principals in the Boulder Valley and Saint Vrain Valley School Districts. Only those children meeting the following four criteria were referred to us. First, only children between 7.5 and 12 years of age were considered. Second, as measured by standardized reading tests administered in the schools, the child had to be reading at a level equal to or less than one-half the expected grade level (e.g., a child in the fourth grade reading at or below second grade level). Third, the child had to have an intelligence quotient of at least 90 on any of the standardized tests administered by the school. Fourth, we required that the child be living with both biological parents. Controls (children with no reported reading problem and making average progress in school (were

matched to the RD children on the basis of age, sex, grade, school, home neighborhood, and, if possible, father's occupational level.

Initial contact letters briefly describing the study and asking for permission to check their child's school records were sent to all parents. After permission was granted, a project staff member checked the records to verify that the above criteria were met and that there was no evidence of neurological damage or of auditory or visual acuity problems. Possible control children were excluded if the records indicated that they were in any way handicapped in reading. Families which met these criteria were then contacted by phone and scheduled for testing. Throughout the study, the proband and both parents were tested. During the first 2 years a limit of two siblings closest in age to the proband and between 7 and 18 years old was established. This was done in hopes of contacting a large number of families and because of financial limitations. During the third year, all siblings between 7 and 18 years old were tested. In addition, siblings not included initially and who still met the age criterion were contacted to participate in the study. Preliminary genetic analyses indicated that the informational quality of the data base could be enhanced by including all sibs of appropriate ages. Furthermore, during the third year, it became increasingly harder to ascertain affected families meeting our criteria. Thus extra funds were available to test more than two siblings per family.

## Tests

Two test batteries of cognitive and perceptual tasks were used. One was designed for subjects under 10 years of age, while the other was composed of tests suitable for subjects 10 and older. Several tests were suitable for all ages and were used in both batteries; when this was not possible, comparable tests were used. After the initial year of testing, the batteries were reduced and only those tests which had high reliability and which discriminated between affected and control groups were retained (Foch, 1975). The list in Table I presents the nine tests in the reduced batteries common to all subjects which were analyzed in the present study.

## Testing Procedures

All subjects were tested by trained examiners at the Institute for Behavioral Genetics. The majority of the testing was done between the hours of 8 a.m. and 5 p.m. on weekends, although some took place during weekdays and weekday evenings. Family members were tested either during the same session or within several weeks of each other.

**Table I.** Colorado Family Reading Study Tests Common to All Subjects

| |
|---|
| Peabody Individual Achievement Test (PIAT) |
| Mathematics (MATH) |
| Reading Recognition (RREC) |
| Reading Comprehension (RCOMP) |
| Spelling (SPELL) |
| Institute for Personality and Ability Testing Nonverbal Culture Fair Intelligence Test (IPAT) |
| Illinois Test of Psycholinguistic Ability—Subtest Auditory Closure (AUDCLSR) |
| Colorado Perceptual Speed Test: Rotatable Letters and Numbers (PSPEED) |
| Wechsler Intelligence Scale for Children—Subtest Coding (CODE) |
| Primary Mental Abilities—Subtest Spatial Relations (PMA) |

The first 58 matched pairs of families were given the unreduced test batteries, and test sessions were divided into three 1-hr blocks separated by 10-min breaks for rest and refreshment. The additional families were given the reduced batteries during test sessions, which were divided into two 1-hr blocks separated by a 10-min break. On arrival for testing, subjects turned in a completed questionnaire containing developmental and medical history information. After all family members were tested, $10 was paid to each individual.

## Analyses

### *Preliminary Analyses*

Prior to performing segregation analyses, several preliminary analyses were performed. In order to adjust the test data for age differences, each subject's score was expressed as a deviation from a regression line (quadratic regression of members of control families on age). Separate age adjustments were employed for children under 10 years of age, for older children, and for adults. In order to facilitate comparison among tests, age-adjusted data were transformed to $T$ scores, yielding a mean of 50 and a standard deviation of 10 for control subjects in each of the three age groups.

Using age-adjusted data on all control individuals, the data were next tested for skewness. A finding of significant skewness would suggest that a power transformation may be advisable, since if the data are skewed, one could falsely conclude the existence of a major gene under certain types of analysis (MacClean *et al.*, 1975).

Next, a multivariate analysis of variance was performed on the probands to look for significant sex, dysfunction (in this case, affected RD proband vs. control proband), and sex $\times$ dysfunction effects. A significant

interaction would indicate that the data of each sex must be analyzed separately. If a significant sex difference, but no interaction, was found, the female data were adjusted so as to have the same mean and variance as the male data as follows:

$$x_f' = (s_m/s_f)(x_f - \bar{x}_f) + \bar{x}_m$$

where $x_f'$ is the new female score, $s_m$ is the standard deviation of the male group, $s_f$ is the standard deviation of the female group, $x_f$ is the original female score, $\bar{x}_f$ is the mean score of the female group, and, $\bar{x}_m$ is the mean score of the male group.

Then two-group discriminant analyses were performed on the probands and controls, the discriminant scores based on these analyses being calculated for all subjects and used as the phenotypic measure for the genetic analyses.

Finally, a search for evidence of sex linkage was undertaken. Father–son (fs), mother–daughter (md), father–daughter (fd), and mother–son (ms) correlations of the discriminant score were compared. Sex linkage is suggested if the relationships $0 \approx \text{fs} < \text{md} < \text{fd} \approx \text{ms}$ are found.

### *Genetic Segregation Analyses*

Classical segregation analysis, as discussed by Morton (1958), assumes that the trait under study can easily be dichotomized or trichotomized. This poses no problem when studying blood groups or certain genetic diseases. However, traits such as RD which can be measured only quantitatively cannot as easily be categorized.

That a trait is continuously distributed does not deny the possibility that segregation at a single genetic locus can account for most of the genetypic variation in the trait. In developing a general model for the analysis of pedigree data, Elston and Stewart (1971) introduced a way of detecting whether the distribution of a quantitative variable is consistent with the involvement of a major gene. The computer program GENSEG incorporates the basic theory and allows as options several likelihood models for performing segregation analysis on families with a maximum of two-generational data (Elston and Yelverton, 1975). The models programmed allow for up to two autosomal loci and one sex-linked locus, normal or dichotomous phenotypic distributions, and various ascertainment functions. Random mating, Hardy-Weinberg frequencies, and no selection are assumed.

The likelihood for a two-generational family is a complex expression containing a number of parameters. All parameters may be estimated simultaneously (the unrestricted model) or a few may be estimated

simultaneously imposing appropriate restrictions on the others. This aspect makes its easy to test any particular null hypothesis by using the likelihood ratio criterion (Kendall and Stuart, 1973).

The segregation analyses of reading study data reported here use a continuous phenotypic measure (the discriminant score discussed above) which is assumed to be normally distributed for each genotype; it is also assumed that the probability that an individual is a proband is adequately described by an exponential function of the discriminant score (i.e., an exponential ascertainment function is assumed) (Elston and Yelverton, 1975). A recent modification (Elston and Sobel, 1979) allowing for ascertainment such that only a select subset of individuals could be probands (e.g., children between 7.5 and 12 years of age, by virtue of the study design) was used in this analysis.

Five hypotheses based on a one-locus autosomal model were tested. The maximum likelihood of the data for the unrestricted case and for each alternative hypothesis was obtained and used for significance testing. Each hypothesis is equivalent to imposing one or more restrictions on the underlying model, and causes the likelihood to be smaller than in the unrestricted cases. Twice the absolute difference in the natural logarithms of the two likelihoods is asymptotically distributed as a $\chi^2$ under the corresponding hypothesis, the degrees of freedom being equal to the number of independent restrictions imposed.

The parameters included in the likelihood expression for one autosomal locus appear in Table II. The five hypotheses, which place restrictions on some of these parameters, are included in Table III.

Several recent articles have applied these methods to different phenotypes (Elston *et al.*, 1974, 1975, 1978) and the efficiency and robust-

**Table II.** Parameters in Likelihood Expression

| Parameter | Description |
|---|---|
| 1. $q$ | gene frequency for allele D; the frequency for the other allele(s) is 1-q |
| 2. $\mu_{DD}$ | mean of phenotypic distribution for DD individuals |
| 3. $\mu_{Dd}$ | mean of phenotypic distribution for Dd individuals |
| 4. $\mu_{dd}$ | mean of phenotypic distribution for dd individuals |
| 5. $\sigma^2$ | variance of each distribution |
| 6. $\tau_{DD\ D}$ | transmission probability; probability that parents DD should transmit D to their offspring |
| 7. $\tau_{Dd\ D}$ | transmission probability; probability that parents Dd should transmit D to their offspring |
| 8. $\tau_{dd\ D}$ | transmission probability; probability that parents dd should transmit D to their offspring |

**Table III.** One-Locus Hypotheses

| Restriction(s) imposed | Hypothesis tested |
|---|---|
| A. $\mu_{DD} = \mu_{Dd}$; $\tau_{DD\,D} = 1.0$, $\tau_{Dd\,D} = 0.5$, $\tau_{dd\,D} = 0$ | Mendelian segregation at a single autosomal dominant locus with two alleles |
| B. $\mu_{Dd} = \mu_{dd}$; $\tau_{DD\,D} = 1.0$, $\tau_{Dd\,D} = 0.5$, $\tau_{dd\,D} = 0$ | Mendelian segregation at a single autosomal recessive locus with two alleles |
| C. $\mu_{DD} = \mu_{Dd}$, or $\mu_{Dd} = \mu_{dd}$[a] | It is sufficient to postulate two rather than three phenotypic distributions |
| D. $\tau_{DD\,D} = 1.0$, $\tau_{Dd\,D} = 0.5$, $\tau_{dd\,D} = 0$ | Mendelian segregation at a single autosomal locus with two alleles |
| E. $\tau_{DD\,D} = \tau_{Dd\,D} = \tau_{dd\,D}$; $\mu_{DD} = \mu_{Dd}$ or $\mu_{Dd} = \mu_{dd}$[a] | That an individual is of a particular type is independent of his parent's type, i.e., there is no specific transmission involved |

[a] The equality used is the one that yields the larger value of the log likelihood.

ness of the methods have been examined in simulation studies (Go *et al.*, 1978).

### *Genetic Heterogeneity*

It is possible that RD is genetically heterogeneous (Finucci *et al.*, 1976). If this is the case, some types may be autosomal, some sex-linked, and some polygenically determined. One way to approach the problem of genetic heterogeneity is to divide the data set into various groups and search for major genes within each group. Thus, in addition to the entire data set being subjected to the above mentioned analyses, three subsets of the family data were reanalyzed. The three subsets were families with male probands, families with female probands, and families with the most severely affected probands (probands with discriminant scores in the lowest third of the distribution).

The discriminant scores generated when including all probands were used for GENSEG to analyze the total data set and families with the most severely affected probands. Two additional discriminant analyses were performed: one using affected male probands and their controls, and one using affected female probands and their controls. Results of these last two analyses were applied to relatives of male probands and female probands, respectively, to obtain discriminant scores.

### *Adult Form Versus Childhood Form of RD*

An option in GENSEG permitting omission of parental data from the analysis (i.e., include only data from one generation) was also used. It is

particularly advantageous to use this option, since it is possible that adults compensate for the reading handicap they had as a child (Critchley, 1970). This analysis provides a test of whether or not our measure of reading disability is really suitable for parents. If similar results are obtained from GENSEG when including and excluding the parents, then it could be concluded that RD persists in the same form throughout life. For this analysis, the discriminant scores generated when including all probands were used.

In summary, segregation analyses were thus applied to five data sets: all families, families with male probands, families with female probands, families with severely affected probands, and children only.

## RESULTS

### Preliminary Analyses

Significant skewness of seven of the variables suggested transformations of the form $x^{1/2}$ for PSPEED; $x^{3/2}$ for MATH, RREC, and SPELL; $x^{7/4}$ for AUDCLSR; and $x^2$ for RCOMP and IPAT; where $x$ is the age-adjusted test score.

A comparison of familial correlations of the discriminant score indicated no evidence of sex linkage. For families with affected probands, the observed correlations were fs = 0.15, md = 0.35, fd = 0.46, and ms = 0.32. For control families, the correlations were 0.19, 0.36, 0.18, and 0.25, respectively. Although the low father–son correlations are suggestive, the hypothesis of a clear-cut $x$-linked locus had to be rejected.

A multivariate analysis of variance (MANOVA) of probands and controls indicated a highly significant sex effect ($F_{9,\ 240} = 6.02$, $p < 0.0001$), a finding completely consistent with the results of previous analyses (DeFries *et al.*, 1978). Thus the female data were transformed using the method described earlier. Adjustments were made within each of six groups—mothers of probands standardized to fathers of probands, sisters of probands standardized to brothers of probands, female probands standardized to male probands, and the three analogous corrections for the control population.

Results for the MANOVA also indicated a significant dysfunction effect ($F_{9,\ 240} = 46.25$, $p < 0.0001$). This is expected since affected probands perform less well on all variables than do control probands. The MANOVA interaction between sex and dysfunction was not significant ($F_{9,\ 240} = 0.90$, $p < 0.52$). Thus the data for the two sexes were pooled for subsequent analyses.

Three two-group discriminant function analyses were performed on the data. One used all affected probands (females and males) as one group and

**Table IV.** Discriminant Function Analyses[a]

| Test | Discriminant weights for standardized variables | | |
|---|---|---|---|
| | Total | Males | Females |
| MATH | 0.104 | 0.015 | 0.395 |
| RREC | 1.038 | 1.046 | 1.307 |
| RCOMP | 0.323 | 0.398 | −0.055 |
| SPELL | 0.228 | 0.191 | 0.281 |
| IPAT | 0.271 | 0.284 | 0.189 |
| CODE | 0.068 | 0.027 | 0.219 |
| PMA | −0.095 | −0.017 | −0.387 |
| PSPEED | 0.102 | 0.131 | 0.091 |
| AUDCLSR | −0.107 | −0.117 | −0.141 |

[a] See Table I for abbreviation of tests.

all control probands as the other, whereas the other two were performed on females and males separately. Standardized discriminant weights generated from the three analyses are presented in Table IV. Ninety-three percent of the probands and controls (total sample) were classified into their assigned group by the discriminant function. Corresponding correct classifications for female and male only were 93% and 92%, respectively.

For all three discriminant analyses, reading recognition had the highest weight, being more than twice as large as any other weight. In general, the weights, when including both sexes and when including only males, are very similar. A slightly different pattern was obtained for the female-only analysis. Whereas math, coding, and PMA have fairly high weights for females, the weights are close to zero for males. Males, however, have a nonzero weight for comprehension in comparison to the near zero weight females have. It is possible that these differences may be attributed to sample size ($N$ = 198 for males, $N$ = 60 for females).

## Segregation Analysis

As Go *et al.* (1978) have indicated, it is important to demonstrate that a mixture of two normal distributions fit the data significantly better than one normal distribution before testing for a major gene effect. Such a test was made for each of the five data sets and positive results were found in each case. Thus segregation analyses were performed on each set of data.

The results of the segregation analyses are summarized in Tables V–IX. Maximum likelihood estimates of all the parameters both under the

**Table V.** Maximum Likelihood Estimates and Differences in Log Likelihoods for the Complete Data Set

| Parameter | Unrestricted model | (A) $\tau$'s Mendelian; $\mu_{DD} = \mu_{Dd}$ | (B) $\tau$'s Mendelian; $\mu_{Dd} = \mu_{dd}$ | (C) $\mu_{Dd} = \mu_{dd}$ | (D) $\tau$'s Mendelian | (E) $\tau$'s equal; $\mu_{Dd} = \mu_{dd}$ |
|---|---|---|---|---|---|---|
| q | 0.47 | 0.15 | 0.58 | 0.61 | 0.55 | 0.66 |
| $\mu_{DD}$ | −1.30 | −0.74 | −0.81 | −0.90 | −1.02 | −0.86 |
| $\mu_{Dd}$ | 0.60 | −0.74 | 1.30 | 1.44 | 1.52 | 1.47 |
| $\mu_{dd}$ | 2.30 | 0.87 | 1.30 | 1.44 | −0.19 | 1.47 |
| $\sigma^2$ | 0.74 | 1.58 | 1.17 | 1.06 | 0.99 | 1.08 |
| $\tau_{DD\ D}$ | 0.97 | 1.00 | 1.00 | 1.00[a] | 1.00 | 0.85 |
| $\tau_{Dd\ D}$ | 0.68 | 0.50 | 0.50 | 0.72 | 0.50 | 0.85 |
| $\tau_{dd\ D}$ | 0.43 | 0.00 | 0.00 | 0.72 | 0.00 | 0.85 |
| Twice the difference in log likelihoods | 0 | 57.42 | 37.08 | 7.33 | 17.50 | 30.28 |
| Degrees of freedom | — | 4 | 4 | 1–2[b] | 3 | 3 |

[a] Parameter converged to a bound.

[b] When a parameter estimate converges to a bound, the distribution of twice the difference in log likelihood is bounded by two $\chi^2$ distributions with the indicated degrees of freedom; these are obtained by adding to the degrees of freedom when the bound is reached under the null hypothesis and subtracting from them when the bound is reached under the unrestricted model. Zero degrees of freedom indicates that no lower bound can be given.

**Table VI.** Maximum Likelihood Estimates and Differences in Log Likelihoods for Families with Male Probands

| Parameter | Unrestricted model | (A) $\tau$'s Mendelian; $\mu_{DD} = \mu_{Dd}$ | (B) $\tau$'s Mendelian; $\mu_{Dd} = \mu_{dd}$ | (C) $\mu_{Dd} = \mu_{dd}$ | (D) $\tau$'s Mendelian | (E) $\tau$'s equal; $\mu_{Dd} = \mu_{dd}$ |
|---|---|---|---|---|---|---|
| $q$ | 0.45 | 0.14 | 0.53 | 0.57 | 0.51 | 0.62 |
| $\mu_{DD}$ | −1.31 | −0.61 | −0.78 | −0.88 | −0.99 | −0.86 |
| $\mu_{Dd}$ | 1.61 | −0.61 | 1.29 | 1.38 | 1.51 | 1.39 |
| $\mu_{dd}$ | −0.32 | 0.90 | 1.29 | 1.38 | −0.15 | 1.39 |
| $\sigma^2$ | 0.92 | 1.50 | 1.06 | 0.98 | 0.92 | 1.00 |
| $\tau_{DD\ D}$ | 0.98 | 1.00 | 1.00 | 1.00[a] | 1.00 | 0.82 |
| $\tau_{Dd\ D}$ | 0.16 | 0.50 | 0.50 | 0.70 | 0.50 | 0.82 |
| $\tau_{dd\ D}$ | 0.0[a] | 0.00 | 0.00 | 0.70 | 0.00 | 0.82 |
| Twice the difference in log likelihoods | 0 | 45.93 | 28.55 | 4.52 | 13.08 | 20.74 |
| Degrees of Freedom | — | 3–4[b] | 3–4[b] | 0–2[b] | 2–3[b] | 2–3[b] |

[a,b] See Table V.

**Table VII.** Maximum Likelihood Estimates and Differences in Log Likelihoods for Families with Female Probands

| Parameter | Unrestricted model | (A) $\tau$'s Mendelian; $\mu_{DD} = \mu_{Dd}$ | (B) $\tau$'s Mendelian; $\mu_{Dd} = \mu_{dd}$ | (C) $\mu_{Dd} = \mu_{dd}$ | (D) $\tau$'s Mendelian | (E) $\tau$'s equal; $\mu_{Dd} = \mu_{dd}$ |
|---|---|---|---|---|---|---|
| $q$ | 0.74 | 0.34 | 0.75 | 0.76 | 0.72 | 0.82 |
| $\mu_{DD}$ | −1.03 | −0.93 | −0.91 | −1.00 | −0.99 | −0.92 |
| $\mu_{Dd}$ | 1.59 | −0.93 | 1.64 | 1.83 | 1.41 | 2.06 |
| $\mu_{dd}$ | 3.99 | 1.32 | 1.64 | 1.83 | 3.91 | 2.06 |
| $\sigma^2$ | 1.51 | 2.00 | 1.82 | 1.64 | 1.60 | 1.66 |
| $\tau_{DD\ D}$ | 1.00[a] | 1.00 | 1.00 | 1.00[a] | 1.00 | 0.91 |
| $\tau_{Dd\ D}$ | 0.69 | 0.50 | 0.50 | 0.72 | 0.50 | 0.91 |
| $\tau_{dd\ D}$ | 0.00 | 0.00 | 0.00 | 0.72 | 0.00 | 0.91 |
| Twice the difference in log likelihoods | 0 | 8.59 | 5.08 | 1.34 | 2.54 | 7.38 |
| Degrees of freedom | — | 2–4[b] | 2–4[b] | 0–2[b] | 1–3[b] | 1–3[b] |

[a,b] See Table V.

unrestricted model and under each hypothesis discussed above are included. In addition, twice the difference between each maximum log likelihood and that obtained for the corresponding unrestricted model is given in the tables. To test the corresponding hypothesis, each reported difference is compared with a $\chi^2$ with the indicated number of degrees of freedom. A significant $\chi^2$ value indicates poor agreement between the unrestricted model and the hypothesis, and hence grounds for rejecting the specific hypothesis.

Table V includes results for the analyses for all families with affected probands (133 families, 566 individuals). In all cases, the $\chi^2$ for testing hypotheses is highly significant. Thus each of the five hypotheses must be rejected. Neither the particular one-locus genetic models specified in GENSEG nor the environmental hypothesis fit these data. It is possible that a more complicated genetic model must be specified.

Results of the segregation analyses for families with male probands (102 families, 431 individuals) are summarized in Table VI. All hypotheses, except possibly that more than two groups need be postulated, were rejected because of the significant $\chi^2$ values. The results obtained are similar to those found for the complete data set. Since all but 31 of our 133 families were ascertained through an affected male, this is not surprising.

More discriminating results were obtained from the analyses for families with female probands (31 families, 135 individuals). Whereas we cannot say anything about the significance of the $\chi^2$ value ($\chi_{0\text{-}2} = 1.34$, $p < 0.1$) obtained to test hypothesis C, that two distributions, rather than three, adequately represent the data, the Mendelian recessive (B) hypothesis cannot be rejected (Table VII). On the other hand, the hypotheses of Mendelian dominant inheritance (A) and of no transmission (E) are significantly less likely. These analyses are based on a smaller number of families and individuals, and it might be thought that the lack of significance of the Mendelian hypotheses (B and D) is merely a function of this fact. Further inspection of the results, however, would argue against this interpretation. First, it should be noted that the estimates of the transmission probabilities under the unrestricted model in Table VII (1, 0.69, and 0) are closer to the Mendelian null hypothesis values (1, 0.5, and 0) than are the analogous estimates in either Table V or Table VI. Second, if the mode of transmission is the same in the two sets of data, we should expect the $\chi^2$ values from each to be approximately proportional to the number of informational units it contains. Now, whether we consider the family or the individual to be the informational unit, the families with male probands compose 76% of the sample, and the families with female probands 24%. It is easily verified that 76% of all the log likelihood differences in Table V are approximately equal to those in Table VI, suggesting that the smaller values in Table VI are due merely to the diminution in sample size. But 24% of the values in Table V

**Table VIII.** Maximum Likelihood Estimates and Differences in Log Likelihoods for Severely Affected Probands

| Parameter | Unrestricted model | (A) $\tau$'s Mendelian; $\mu_{DD} = \mu_{Dd}$ | (B) $\tau$'s Mendelian; $\mu_{Dd} = \mu_{dd}$ | (C) $\mu_{Dd} = \mu_{dd}$ | (D) $\tau$'s Mendelian | (E) $\tau$'s equal; $\mu_{Dd} = \mu_{dd}$ |
|---|---|---|---|---|---|---|
| $q$ | 0.23 | 0.40 | 0.62 | 0.64 | 0.64 | 0.70 |
| $\mu_{DD}$ | −1.60 | −0.92 | −1.33 | −1.51 | −1.39 | −1.48 |
| $\mu_{Dd}$ | −1.50 | −0.92 | 1.30 | 1.22 | 1.33 | 1.24 |
| $\mu_{dd}$ | 1.22 | 1.71 | 1.30 | 1.22 | −1.00 | 1.24 |
| $\sigma_S$ | 0.92 | 1.40 | 1.02 | 0.92 | 1.02 | 0.94 |
| $\tau_{DD\ D}$ | 0.16 | 1.00 | 1.00 | 0.96 | 1.00 | 0.83 |
| $\tau_{Dd\ D}$ | 0.76 | 0.50 | 0.50 | 0.58 | 0.50 | 0.83 |
| $\tau_{dd\ D}$ | 0.24 | 0.00 | 0.00 | 1.00[a] | 0.00 | 0.83 |
| Twice the difference in log likelihoods | 0 | 24.54 | 12.99 | 0.58 | 7.49 | 7.42 |
| Degrees of Freedom | — | 4 | 4 | 1–2[b] | 3 | 3 |

[a,b] See Table V.

are approximately equal to the values in Table VII for hypotheses C and E only. The values expected for the Mendelian hypotheses B and D on the basis of just smaller sample size (8.90 and 4.20) are appreciably larger than the nonsignificant values actually observed (5.08 and 2.54), suggesting a real difference in the overall mode of transmission for this subset of the data.

The fourth data set analyzed with GENSEG was that which included families with the most severely affected probands (44 families, 188 individuals). Both the dominant and recessive Mendelian hypotheses are highly unlikely to occur ($p < 0.0001$ in both cases; see Table VIII). The three distribution Mendelian and the environmental hypotheses cannot be rejected and, in fact, are equally likely explanations of the data. But whereas the $\chi^2$ for the Mendelian hypothesis D is somewhat larger than that expected on the basis of sample size diminution (7.49 versus 5.78), that for no transmission is smaller (7.42 vs. 9.99). This would argue more in favor of there being no genetic transmission of our discriminant score in these families. A positive finding is that hypothesis C—two distributions—can adequately explain the data ($\chi_{1\text{-}2} = 0.58, p > 0.4$; smaller than the value 2.42 expected on the basis of smaller sample size alone).

Results summarized in Table IX indicate the slightly different findings which emerged from analyzing the data of children only (133 families; 301 individuals). Hypotheses A and B can be rejected ($\chi^2_{3\text{-}4} = 11.85, p < 0.001$, and $\chi^2_{3\text{-}4} = 13.56, p < 0.0001$, respectively), but hypothesis D cannot. Thus although neither a dominant nor a recessive model (hypothesis A or B) fits the data, a model which postulates Mendelian inheritance with three phenotypic distributions cannot be rejected. Apparent support of familial transmission of RD is found as a result of being able to reject hypothesis E, the "lack of vertical transmission" hypothesis ($\chi^2_{2\text{-}3} = 10.78, p < 0.0001$); but hypothesis E could be rejected merely because it postulates two distributions, whereas hypothesis D postulates three distributions. In fact, a comparison of the likelihoods obtained from hypotheses C and E ($\chi^2_{1\text{-}2} = 0.96$) shows that the lack of fit of E is mainly due to the lack of fit of two distributions. This also suggests that an environmental hypothesis is more likely (but not significantly so) than the genetic models A and B. In this case, we cannot make a comparison with a fraction of the $\chi^2$ values obtained for the total sample, since an analysis of children alone may be inherently different in power.

Hypothesis D concerns Mendelian segregation at a single autosomal locus without complete dominance. However, a good fit to this hypothesis could also result from polygenic or common-family environmental effects. Major-gene involvement would be more convincing if hypothesis A were much more likely than hypothesis B, or *vice versa* (Go *et al.*, 1978). The

**Table IX.** Maximum Likelihood Estimates and Differences in Log Likelihoods for Children Only

| Parameter | Unrestricted model | (A) $\tau$'s Mendelian; $\mu_{DD} = \mu_{Dd}$ | (B) $\tau$'s Mendelian; $\mu_{Dd} = \mu_{dd}$ | (C) $\mu_{DD} = \mu_{Dd}$ | (D) $\tau$'s Mendelian | (E) $\tau$'s equal; $\mu_{DD} = \mu_{Dd}$ |
|---|---|---|---|---|---|---|
| $q$ | 0.54 | 0.46 | 0.82 | 0.41 | 0.47 | 1.00[a] |
| $\mu_{DD}$ | −1.08 | −0.52 | −0.51 | −0.56 | 1.12 | −0.56 |
| $\mu_{Dd}$ | 0.52 | −0.52 | 2.20 | −0.56 | 0.18 | −0.56 |
| $\mu_{dd}$ | 2.91 | 2.24 | 2.20 | 2.15 | 2.67 | 2.17 |
| $\sigma_2$ | 0.60 | 0.95 | 0.95 | 0.94 | 0.64 | 0.94 |
| $\tau_{DD\ D}$ | 1.00[a] | 1.00 | 1.00 | 1.00[a] | 1.00 | 0.56 |
| $\tau_{Dd\ D}$ | 0.49 | 0.50 | 0.50 | 0.44 | 0.50 | 0.56 |
| $\tau_{dd\ D}$ | 0.49 | 0.00 | 0.00 | 0.43 | 0.00 | 0.56 |
| Twice the difference in log likelihoods | 0 | 11.85 | 13.56 | 9.82 | 4.46 | 10.78 |
| Degrees of freedom | — | 3–4[b] | 3–4[b] | 0–2[b] | 2–3[b] | 2–3[b] |

[a,b] See Table V.

**Table X.** Mean Discriminant Scores of Relatives of Affected Probands

| | Male proband | | Female proband | | |
|---|---|---|---|---|---|
| Relationship | Mean | *N* | Mean | *N* | † |
| Father | 0.46 | 101 | 0.02 | 30 | 1.26 |
| Mother | 0.48 | 102 | −0.18 | 31 | 1.91[a] |
| Brother | 0.02 | 60 | −0.34 | 27 | 0.99 |
| Sister | −0.04 | 67 | −0.13 | 16 | 0.22 |

[a] $p < 0.05$.

only analysis in which one of these two hypotheses is rejected and the other not is the analysis pertaining to the families of the female probands.

Using the theory outlined by Carter (1969, 1973), a preliminary test of fit to a polygenic threshold model can be attempted. The theory states that when a disorder effects one sex less frequently than the other (females in the case of RD) a greater proportion of relatives of female probands should be affected. This is the case, since females must possess a greater number of the "risk genes" to be affected and hence their relatives have more of these genes than do relatives of males.

Mean discriminant scores of relatives of male and female affected probands were compared to test for a polygenic threshold model to explain the familial nature of RD. A lower mean score would indicate a greater proportion of affected individuals. Results of *t* tests did not provide strong evidence to support this hypothesis (see Table X). The only significant difference between relatives of male and female probands was for mothers. However, in every case, relatives of female probands have lower scores, again suggesting transmission (whether monogenic or polygenic) in the families of female probands.

## DISCUSSION

Findings from the MANOVA indicated a highly significant sex effect, a highly significant dysfunction effect, and a nonsignificant sex × dysfunction interaction. The significant sex effect, which has been documented elsewhere (DeFries *et al.*, 1978), made an appropriate adjustment necessary so that data of both sexes could be analyzed simultaneously. The significant dysfunction effect demonstrates that we were successful in finding severely reading-disabled children and matching them to children making normal progress in school. The nonsignificant interaction suggests that the disability, as measured by our discriminant score, is not more severe in

probands of one or the other sex. However, it should be noted that 3 times as many affected male probands were ascertained.

Results of all three discriminant function analyses indicated that reading recognition is the test of most importance in separating normal from disabled readers. In general, the patterns of weights are essentially the same for two of the three analyses (total and male probands). The weights generated from the female data only may differ from the other two simply as a function of sample size. It should be noted that the weights for RCOMP, SPELL, and IPAT are also significant contributors in the discrimination between normal and disabled readers. Thus, although the disability is largely attributed to reading, it is not specific to it. On the basis of these analyses, there is no reason to conclude that the pattern of the disability is different in the two sexes. This is in accord with the finding of no significant interaction in the MANOVA.

Segregation analyses were performed on the total data set, on families with male probands, on families with female probands, on families with severely affected probands, and on all children. The results of the first four could be compared as a preliminary investigation of genetic heterogeneity of RD. A comparison of the first and fifth analyses could help elucidate the stability of a reading handicap throughout life.

A summary of the results of the segregation analyses appears in Table XI. It can be seen that none of the models tested could explain the data for either the complete data set or the families with male probands. Two explanations exist—a more complicated model needs to be postulated or RD is a genetically heterogeneous disorder. In the latter case, we should expect the analyses of each data set to reflect the major, rather than the only, cause of RD in that data set.

The most likely interpretation of the data from families of female probands is that of recessive inheritance. The data are consistent with a recessive gene being the major cause of RD in females, but accounting for only a small proportion of the cases in males. This may explain the distorted sex ratio observed in the prevalence of RD.

Environmental determination of RD is the most plausible explanation for the majority of but not all cases in the severely affected probands data set. It should be noted that the discriminant score used here to define severely affected probands is the same one which best discriminates between the RD probands and control. This function includes factors other than reading. For instance, our nonverbal measure of IQ is weighted positively. Thus those identified as most severely affected might also be those with lowest IQ. This might be a possible explanation for finding that the environmental hypothesis could not be rejected in the severe proband subset.

**Table XI.** Results of Genetic Analyses

| Hypothesis | Data set | | | | |
|---|---|---|---|---|---|
| | Total group | Male probands | Female probands | Severely affected probands | Children only |
| A. Dominant | Reject | Reject | Less likely | Reject | Reject |
| B. Recessive | Reject | Reject | Most likely | Reject | Reject |
| C. Two distribution | Reject | Inconclusive | Inconclusive | Do not reject | Inconclusive |
| D. Mendelian incomplete dominance | Reject | Reject | Do not reject | Less likely | Most likely |
| E. Environmental (within families) | Reject | Reject | Less likely | Most likely | Reject, but plausible |

Finally, the results of analyzing the children's data separately indicate only that they are consistent with both genetic and environmental determination. This result is different from the results from the total set. However, this analysis may be inherently different from the other analyses in power, and thus it is impossible to make any more detailed comparison of the observed differences.

In conclusion, results of the present analysis support the hypothesis that RD is a genetically heterogeneous disorder. Therefore, segregation analysis of specific RD subtypes, as identified by differential diagnosis, may yield more conclusive evidence either for or against various simple locus models. Such an approach is highly recommended for future research concerning the genetic etiology of RD.

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## REFERENCES

Bakwin, H. (1973). Reading disability in twins. *Dev. Med. Child Neurol.* **15**:184–187.

Belmont, L., and Birch, H. G. (1965). Lateral dominance, lateral awareness and reading disability. *Child Dev.* **36**:57–72.

Carter C. O. (1969). Genetics of common disorders. *Br. Med. Bull.* **25**:52–57.

Carter C. O. (1973). Multifactorial genetic disease. In McKusick, V. A., and Clairborne, R. (eds.), *Medical Genetics*, HP Publishing Company, New York, pp. 199–208.

Critchley, M. (1970). *The Dyslexic Child*, William Heinemann Medical Books, New York.

Crow J. F. (1965). Problems of ascertainment in the analysis of family data. pp. 23–44. In Neel, J. V., Shaw, M. W., and Schull, W. J. (eds.), *Epidemiology and Genetics of Chronic Diseases*, Department of Health, Education and Welfare, Washington, D.C.

DeFries, J. C., Singer, S. M., Foch, T. T., and Lewitter, F. I. (1978). Familial nature of reading disability. *Br. J. Psychiat.* **132**:361–367.

Elston, R. C., and Sobel, E. (1979). Sampling considerations in the gathering and analysis of pedigree data. *Am. J. Hum. Genet.* **31**:62–69.

Elston, R. C., and Stewart, J. (1971). A general model for the genetic analysis of pedigree data. *Hum. Hered.* **21**:523–542.

Elston, R. C., and Yelverton, K. C. (1975). General models for segregation analysis. *Am. J. Hum. Genet.* **27**:31–45.

Elston, R. C., Namboodiri, K. K., Nino, H. V., and Pollitzer, W. S. (1974). Studies on blood and urine glucose in Seminole Indians: Indications for segregation of a major gene. *Am. J. Hum. Genet.* **26**:13–34.

Elston, R. C., Namboodiri, K. K., Gluek, C. J., Fallat, R., Tsang, R., and Leuba, V. (1975). Study of the genetic transmission of hypercholesterolemia and hypertriglyceridemia in a 195 member kindred. *Ann. Hum. Genet.* **39**:67–87.

Elston, R. C., Namboodiri, K. K., Spence, M. A., and Rainer, J. D. (1978). A genetic study of schizophrenia pedigrees. II. One-locus hypotheses. *Neuropsychobiology* **4(4)**:193–206.

Finucci, J. M., Guthrie, J. T., Childs, A. L., Abbey, H., and Childs, B. (1976). The genetics of specific reading disability. *Ann. Hum. Genet.* **40**:1–23.

Fisher, J. H. (1905). Case of congenital word-blindness (inability to learn to read). *Ophthalmol. Rev.* **24**:315–318.
Foch, T. T. (1975). Analysis of the unreduced battery for the Colorado Family Study of Specific Reading Disability. M.A. thesis, University of Colorado.
Go, R. C. P., Elston, R. C., and Kaplan, E. B. (1978). Efficiency and robustness of pedigree segregation analysis. *Am. J. Hum. Genet.* **30**:28–37.
Hallgren, B. (1950). Specific dyslexia. *Acta Psychiatr. Neurol. Suppl.* **65**:1–287.
Hermann, K., and Norrie, E. (1958). Is congenital word-blindness an hereditary type of Gerstmann's syndrome. *Psychiat. Neurol.* **136**:59–73.
Hinshelwood, J. (1907). Four cases of congenital word-blindness occurring in the same family. *Br. Med. J.* **11**:1229–1232.
Kendall, M. G., and Stuart, A. (1973). *The Advanced Theory of Statistics*, Vol. 2, Charles Griffin and Company, London.
Kirk, S. A., and Bateman, B. (1962). Diagnosis and remediation of learning disabilities. *Except. Child* **29**:73–78.
Lenz, W. (1970). *Medizinische Genetik-Grundlagen, Ergebnisse und Probleme*, 2nd ed., Stuttgart, Thieme.
MacClean, C. J., Morton, N. E., and Lew, R. (1975). Analysis of family resemblance. IV. Operational characteristics of segregation analysis. *Am. J. Hum. Genet.* **27**:365–384.
McCarthy, J. J., and McCarthy, J. F. (1969). *Learning Disabilities*, Allyn and Bacon, Boston.
Morgan, W. P. (1896). A case of congenital word-blindness. *Br. Med. J.* **11**:1378.
Morton, N. E. (1958). Segregation analysis in human genetics. *Science* **127**:79–80.
Owen, F. W. (1968). Learning disability—A familial study. *Bull. Orton Soc.* **18**:33–39.
Sladen, B. (1970). Inheritance of dyslexia. *Bull. Orton Soc.* **20**:30–40.
Stephenson, S. (1907). Six cases of congenital word-blindness affecting three generations of one family. *Ophthalmoscope* **5**:482–484.
Symmes, J. S., and Rapoport, J. L. (1972). Unexpected reading failure. *Am. J. Orthopsychiat.* **42**:380–385.
Thomas, C. J. (1905). Congenital "word-blindness" and its treatment. *Ophthalmoscope* **3**:380–385.
Zahalkova, M., Vrzal, V., and Kloboukova, E. (1972). Genetical investigations in dyslexia. *J. Med. Genet.* **9**:48–52.
Zerbin-Rüdin, E. (1967). Congenital word blindness. *Bull. Orton Soc.* **17**:47–54.

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