Familial Dyslexia: Genetic and Medical Findings in Eleven Three-Generation Families

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In addition to providing information on the inheritance of dyslexia, the present study of eleven three-generation families has provided a unique opportunity to

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compare affected and unaffected family members at all ages. The data presented here are based on pedigree information, a questionnaire administered to all participating family members in relation to sex ratio, handedness, the severity of dyslexia by sex, pre- and perinatal complications, medical complications, years of education and earning ability, and a battery of standardized tests to define the presence or absence of dyslexia.

The pattern of inheritance was consistent with the postulated autosomal dominant mode of inheritance and penetrance was found to be > 90 percent. Of 73 individuals determined to have a gene leading to dyslexia, seven were classified as obligate carriers and six as compensated adults who had no current symptoms or diagnostic evidence of dyslexia. The sex ratio (1.06) was not different from the expected ratio of 1.04. Left-handedness, major pre- and perinatal complications, and autoimmune disorders and allergy were not more common in dyslexics than non-dyslexics. The number of years of education and average income were similar in affected and unaffected family members. Compensated adults and obligate carriers were similar to unaffected family members in each of these parameters.

Introduction

Analysis of families with dyslexia in three generations yields a somewhat different view of dyslexia than studies of reading-disabled or dyslexic children. Because ascertainment was by family, pre- and postnatal environmental influences on individuals are minimized and an indirect but long term evaluation of the effects of the presumed gene or genes leading to the diagnosis of dyslexia can be obtained by comparing children and adults who are unaffected with those who are affected over a full range of ages. A unique but appropriate control population also emerges, namely the unaffected family members. Unaffected spouses also serve as a second, or alternative, control sample for affected adults.

The primary purpose of the present study is to detect the gene(s) leading to familial dyslexia and to describe the effects of these genes through neuropsychological, psychophysical, and brain imaging studies. Several preliminary reports of the overall study have been published (Lubs et al. 1988; Lubs et al. 1991a; Lubs et al. 1991b) which describe the diagnostic criteria, questionnaires (medical and educational), gene localization studies and other aspects of the study. The purpose of the present report, however, is to describe the genetic and medical data that have emerged from the eleven families currently under study. Psychological and social data in adults has been reported separately (Feldman et al. 1993a; Lubs et al. 1991a).

Methods

Ascertainment of Families

Over the past four years, families with a documented three-generation history of dyslexia were identified through a variety of referral sources. After an initial telephone interview, families who met all admission criteria were selected for participation. A complete pedigree was obtained, generally through several knowledgeable family members.

Screening and Diagnosis: Only individuals with IQ scores of 90 or above with no known emotional, neurological and/or environmental reasons for reading impairment were accepted into the study. The criteria for the diagnosis of dyslexia were based on age-determined standard deviation discrepancies between IQ and reading and spelling performance on selected standardized tests. The diagnostic screening battery included a standard intelligence test and tests for reading and spelling skills. These were divided into four classes of subtests:

Spelling	Wide range Achievement Test Revised: Spelling subtest
Oral Reading	Gray-Oral Reading Test-Revised
	Woodcock-Johnson Psycho-Educational Battery Letter-Word Identification subtest
Comprehension	Woodcock-Johnson Psycho-Educational Battery Passage Comprehension subtest
Decoding	Woodcock-Johnson Psycho-Educational Battery Word-Attach Scale subtest
	Nonsense Passages (ages 16+)

Criteria for diagnosis of dyslexia change with the age or grade of the child. In the first year of school, a score only half a standard deviation below their expected score (based on IQ) is required in at least one of the four categories. This increases to one standard deviation for the age group 9–14 years, on two of the four categories, and to 1.5 standard deviations on two of the four categories for those age 15 or over. The Nonsense Passages Test (Finucci et al. 1976; Gross-Glenn et al. 1990) was included in adults since it has been shown to be sensitive to residual reading deficits among adult compensated dyslexics, but was not included in the battery for children. These have been described in detail previously (Lubs et al. 1991a; 1991b).

Questionnaire. A comprehensive educational, medical, social, and historical questionnaire was administered by a research associate to affected and unaffected family members. Questions pertained to pre- and perinatal problems, early childhood development, school history including previous diagnosis of learning disability, dyslexia or

other learning problems, medical history including the incidence of immune and autoimmune diseases, academic achievement, speech and language problems, areas of strength and weakness, marital status, and educational/occupational history. Handedness was assessed by direct question, through self-report, and using the Edinburgh Handedness Inventory (Oldfield 1971). Details of the questionnaire have been outlined in a previous report (Lubs et al. 1991b). This information was used to obtain diagnostic information regarding a documented history of reading/spelling problems and to screen individuals with neurological or other conditions which might make them ineligible for the study.

Data Analysis. The questionnaire data were reviewed and analyzed in several ways. The statistical analysis of many parameters comparing adult dyslexics with adult unaffected family members has been previously reported (Feldman et al. 1993a). These data will be referred to briefly in the present report. Data also were inspected using printouts showing data by family and analyzed by the Fisher's exact test for differences between dyslexics and normals and for differences between families. Where age was not a significant or appropriate variable, analyses were carried out comparing all dyslexics (adult and children who were affected or carrying the gene) with unaffected family members and normal spouses using a chi square with Yates correction. Specific studies were also made of compensated adults and obligate carriers; since the numbers of these individuals were small, this consisted only of listings and inspection of data for each class.

Results

Genetics

Partial pedigrees of the eight largest families are shown in Figures 1 and 2. In several families (3000 and 3006) large branches of the families have deferred participation in the study or have not yet been available for study: these branches are not included in the present pedigrees. Family members were determined to have or not have a gene leading to familial dyslexia by a combination of historical data and screening tests. The former were classified either as "affected" (by history and diagnostic criteria), as "compensated adults" (having a clear, documented history of dyslexia but not testing as affected), or as "obligate carriers" (negative by history and testing, but with an affected parent and child). Of 74 determined to have a gene leading to dyslexia, 61 were classified as affected, six as compensated adults, and seven as obligate carriers. All six compensated adults were female and four of seven obligate carriers were female (Table I). Those with a negative ed-

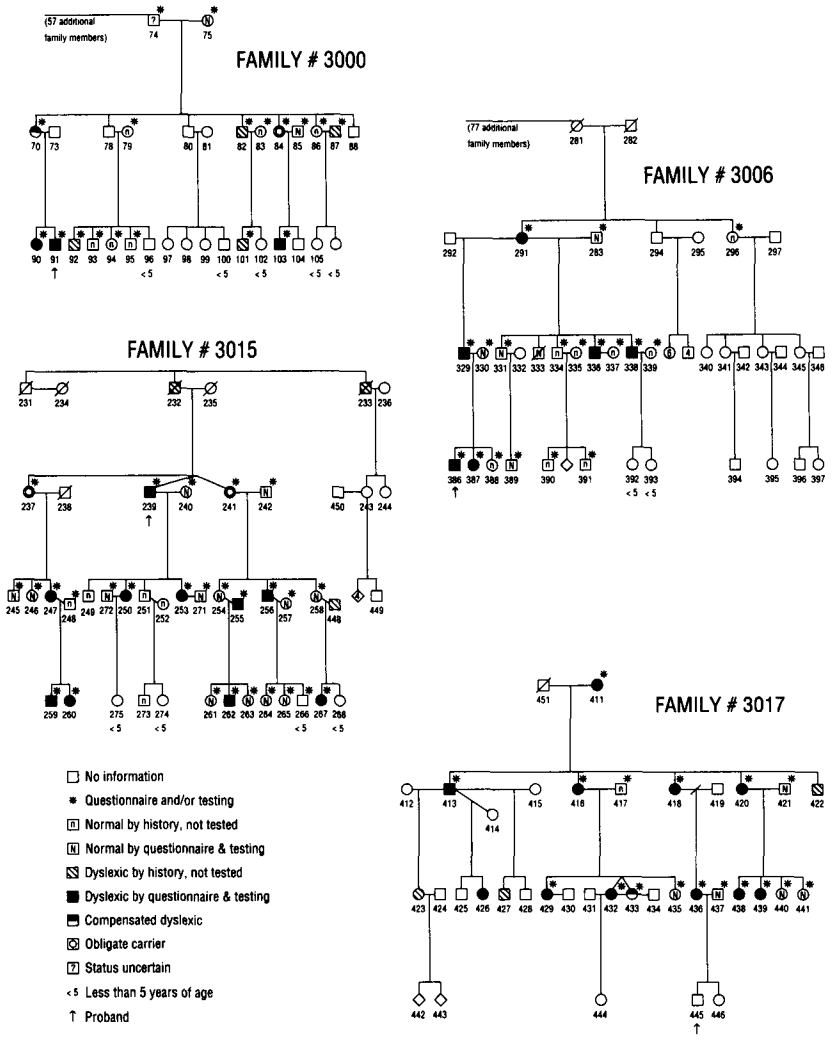

Figure 1. Pedigrees of families #3000, 3006, 3015, and 3017

ucational history of dyslexia and normal screening results were classified as not affected.

A formal segregation analysis to test the hypothesis of autosomal dominant inheritance cannot be done since families were selected for study based on a history of dyslexic family members in three generations. Several points can be made, however, about the mode of inheritance. In the parts of the larger pedigrees, which were not directly involved in ascertainment, such as 3022 and 3015, three generations of

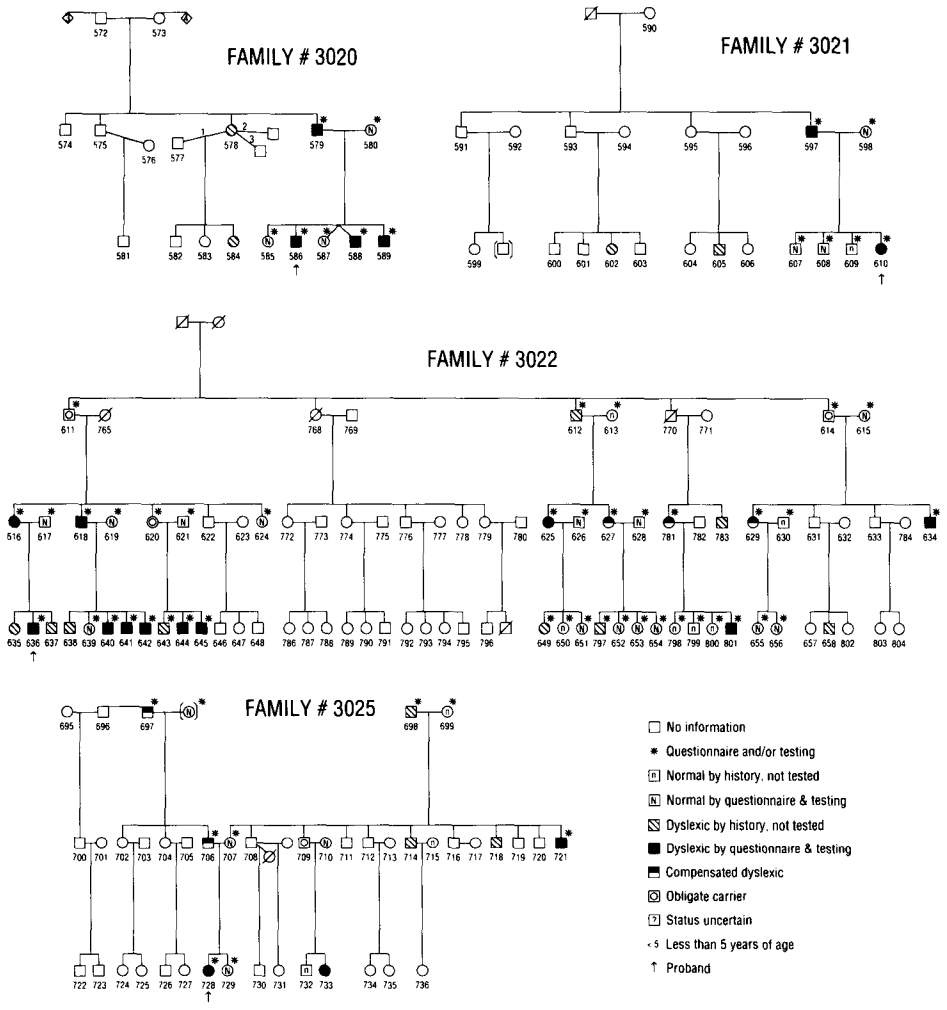

Figure 2. Pedigrees of families #3020, 3021, 3022, and 3025. Note that studies in many family members are still incomplete and that family 3025, which is presented here as one family, will probably be considered as two separate families when the studies are complete. Family 3022 is the family in which linkage with chromosome 15 polymorphisms were originally reported. Linkage has not been confirmed with DNA polymorphisms (Wen et al. 1993).

dyslexics were also seen. The sex ratio was not altered significantly from 1 (see below), and male to male transmission was frequently observed, thus ruling out X-linked dominant inheritance. Proof of autosomal dominant inheritance awaits either the identification of a linkage

Table I
Genetic Data: Distribution of Affected Adults and Children, Compensated Adults, and Obligate Carriers

	Children	Adults					Adults & Children
Family #	# Dyslexic	# Compensated Dyslexics (C)	# Dyslexic (D)	Proportion Compensated C/C+D	# Obligate Carrier (O)	Proportion C *or* O	# C, D, and O
3000	3	1	0	1/1	1	2/2	5
3001	3	1	4	1/5	0	1/5	8
3006	2	0	4	0/4	0	0/4	6
3014	3	0	4	0/4	0	0/4	7
3015	2	0	5	0/5	2	2/7	9
3017	1	1	9	1/10	0	1/10	11
3018	1	0	1	0/1	0	0/1	2
3020	3	0	1	0/1	0	0/1	4
3021	1	0	1	0/1	0	0/1	2
3022	3	3	8	3/11	3	6/14	17
3025	1	0	1	0/1	1	1/2	3
TOTALS	23	6	38	6/44 (14%)	7	13/51 (26%)	74

(the purpose of the study) or development of a specific diagnostic test which would make possible a less biased identification of families.

The observation that seven of 74 (9 percent), of those having a gene leading to dyslexia had no evident effect from it, i.e. the gene was non-penetrant, is consistent with many autosomal dominant disorders in which the non-penetrance rate may be as high as 10 percent. Moreover, if children were excluded (because the possibility that "normal" children might be obligate carriers cannot be ruled out), the frequency was still only 14 percent (7/51). A further six of 51 dyslexics over the age of 21 (who at one time were classified as dyslexic) no longer tested as dyslexic, and were classified as compensated dyslexics. A total of 24 percent of adults were determined to have the gene (12/51); therefore, either never had significant dyslexia or were no longer dyslexic. In other studies involving only parents and twin children, as in the Colorado Reading Project (DeFries et al. 1991), this high frequency of normally functioning adults (one in four in the present study) may have been a significant factor in obscuring possible autosomal dominant inheritance. The milder effect in females (Feldman et al. 1993b), as well as a frequent lack of awareness of dyslexia several decades ago and imprecise diagnostic tests also are likely contributors to falsely negative family histories. The selection of very large three-generation families, on the other hand, allows the identification of obligate carriers and provides a more complete view of the genetics of this common disorder.

One definite and one possible instance of marriage between a non-dyslexic family member and a dyslexic spouse (Nos. 255 and 448 in family 3015) were encountered. These spouses (each of whom had a negative family history) and their children, however, have been omitted from the current analyses. No marriage between a dyslexic family member and dyslexic spouse was encountered. Thus, positive assortative mating, at least in this study, was not a significant factor and does not need to be taken into account in the genetic analysis. Two marriages between dyslexics, of which one couple met in the Orton clinic, were identified in North Carolina, however (Wood et al. 1991). In family 3025, which is still under study, there is a suggestion of dyslexia in families of both 706 and 707. Their children and the relatives of 706 have been excluded from analyses until more family members have been studied.

The male/female ratio in dyslexics (including obligate carriers and compensated dyslexics) was 1.06 (38/36), which was not different from 1.04. Among normal spouses, a similar ratio was observed (14/15). The unusual ratio in normal family members (8/21) reflected the difficulty in enlisting normal male family members in the study, since for adults this involved missing one to six days' work. Inspection of the pedigrees

in Figures 1 and 2, moreover, does not reveal a relative absence of males among unstudied family members. Only in family 3017 was there an unusual sex ratio, with nine of ten dyslexics being female. No normal males entered the study in this family, but six are shown in the pedigree. Family 3017 is different in many parameters, and is the principal family that suggests heterogeneity, particularly in relation to attention deficit disorder and psychiatric diagnoses. This has been briefly presented in a prior report (Lubs et al. 1991b) and very likely represents only a random variation in sex ratio. The final interpretation of possible heterogeneity awaits the results of the gene localization studies now in progress.

Among dyslexics, 13 percent (8/61) were left-handed; 15 percent (11/74) were left-handed if compensated dyslexics and obligate carriers were included. These values did not differ significantly from 14.3 percent in normal family members (4/28), from 10.3 percent in normal spouses (3/29), or from 12.3 percent in the combined sets of normals (7/57) (Table II). An unusually high frequency of left-handedness was not observed in any family (Table III). These data were derived from a direct question relating to handedness, but the Edinburgh Handedness Inventory, which was available on a smaller sample, yielded comparable results.

Prenatal and Perinatal Problems. Possible pre- and perinatal adverse influences were also addressed by questionnaire. Prenatal information was generally available only on the younger family members. No difference in the frequency of prenatal complication between dyslexics (8/26, or 30.1 percent) and all non-dyslexics (5/24, or 21.8 percent) was observed, and there was no suggestion of clustering in any family.

Perinatal Complications. Perinatal complications were more frequently reported in the overall sample of dyslexics (17/65, or 26 percent), including compensated dyslexics and obligate carriers, than in normal family members and spouses (4/56, or 7 percent). Perinatal complications were increased significantly in the sample of dyslexics by Fisher's exact test, $p = .03$. These reports were distributed evenly through all eleven families. Among the 54 dyslexics, the most frequently reported complications were ten premature births (eight were 10–31 days premature, two were 42–56 days premature), and jaundice with transfusion due to blood group incompatibility (in three). Each of the following were reported once: C-section due to fetal distress, "underdeveloped lungs," "cardiopulmonary resuscitation required at birth." One of six compensated dyslexics was a twin and none of six obligate carriers were reported with complications. In contrast, among 28 normal family members there was one multiple birth (breech) and

Table II—Summary Table
Questionnaire Data and Genetic Classification

	WITH DYSLEXIA GENE								WITHOUT DYSLEXIA GENE					
	Dyslexic		Compensated		Obligate Carrier		Yes/Total		Family Member		Spouse		Yes/Total	
Parameter	Yes	No	Yes	No	Yes	No	N	(%)	Yes	No	Yes	No	N	(%)
Female	26	35	6	0	4	3	36/74	(49)	21	8	15	14	36/58	(62)
Right Handed*	53	8	5	1	5	2	63/74	(85)	24	4	26	3	50/57	(88)
Prenatal Complications	7	18	1	0	0	0	8/26	(31)	4	13	0	7	4/24	(17)
Perinatal Complications	16	38	1	5	0	5	17/65	(26)	2	28	2	28	4/56	(7)
Neurol. Complications	12	46	0	6	1	4	13/70	(19)	4	24	6	23	10/57	(18)
Seizures	4	54	1	6	1	4	6/70	(9)	2	26	1	29	3/57	(5)
Allergy	30	28	4	3	2	3	36/70	(51)	17	11	14	15	31/57	(54)
Auto Immune Disorders	13	45	2	5	2	2	18/70	(26)	6	22	6	23	12/57	(21)
Premature Graying	9**	49	0	7	0	5	9/70	(13)	4	24	4	25	8/57	(14)

*Comparable data, but on fewer people, obtained from Edinburgh Handedness Index (Laterality Quotient)
**Note in family 3017 4/8 reported premature graying

Table III
Right-Handedness by Family

	With Dyslexia Gene						No Dyslexia Gene				
	Dyslexic		Compensated		Obligate Carrier		Family Member		Spouse		
Fam. ID	NO·	YES*	NO	YES	NO	YES	NO	YES	NO	YES	TOTAL
3000	1	2	—	1	—	1	—	1	—	2	8
3001	1	6	—	1	—	—	—	1	—	2	11
3006	—	6	—	—	—	—	—	2	1	2	11
3014	2	5	—	—	—	—	—	1	—	3	11
3015	—	7	—	—	1	1	1	5	1	4	20
3017	2	8	—	1	—	—	—	3	—	2	16
3018	—	2	—	—	—	—	—	1	—	3	6
3020	1	3	—	—	—	—	—	2	—	1	7
3021	—	2	—	—	—	—	—	2	—	1	5
3022	1	10	1	2	1	2	3	3	—	5	28
3025	—	2	—	—	—	1	—	3	1	1	8
TOTAL	8	53	1	5	2	5	4	24	3	26	
Total/Class	61		6		7		28		29		131

*Yes = right-handed
·No = non-right-handed

one premature birth (days unspecified). Among 28 normal spouses one was reported as premature. Although the difference between normals and dyslexics (including or excluding compensated adults and obligate carriers) are statistically significant, the clinical importance of the complications in dyslexics is at best only suggestive. In no case was there a clear history of a severe perinatal insult, such as 60–90 days prematurity or anoxia at the level where a clinical effect would be expected. It is likely that these differences represent overreporting by parents looking for an identifiable cause of their child's dyslexia. No difference was found, moreover, among the parents and grandparents (Feldman et al. 1993a), although the data were limited. Even if small effects on brain development occurred, they were not significantly frequent to account for the great majority of dyslexics in these families.

Social Adaptation. The questionnaire data has also been used to compare the long term educational, occupational and social effectiveness in the adult dyslexic and non-dyslexic family members (Feldman et al. 1993a). The results, which show almost no differences in outcome will be summarized here to provide a more complete picture of the long-term significance of this genetic disorder. No differences in income, years of education, or marital status between the dyslexic and nondyslexic individuals were found. Dyslexic family members were not more likely than controls to have drug or alcohol problems. A particularly high frequency of attention deficit disorder with hyperactivity (ADHD, DSM-III) and minor psychiatric symptoms (depression and phobias) were noted. Both were particularly frequent in Family 3017. No other differences were identified by the questionnaire data.

Neurological History. As shown in Table II, the overall frequency of Neurological complaints among dyslexics (19 percent) was the same as in unaffected family members. Similarly, the reported frequency of individuals with seizures was no different in the two groups. Familial dyslexics were not more likely than unaffected family members to have oculomotor or visual problems, right-left confusion or head injuries. There were no reports of Tourette's Syndrome in any of the eleven families.

Autoimmune and Related Disorders. As shown in Tables II and IV, there was no difference between those with and without a gene for dyslexia in relation to the frequency of allergy (51 percent compared to 54 percent), autoimmune disorders (26 percent compared to 21 percent) and premature graying (13 percent compared to 14 percent). As shown in Table IV, there was no obvious clustering of autoimmune disorders in any family, including Family 3017. Premature graying, however, was suggestively increased in Family 3017: of nine reported in-

Table IV
Autoimmune Disorders by Family

	With Dyslexia Gene						No Dyslexia Gene				
	Dyslexic		Compensated		Obligate Carrier		Family Member		Spouse		
Fam. ID	NO·	YES*	NO	YES	NO	YES	NO	YES	NO	YES	TOTAL
3000	3	—	1	—	—	1	1	—	1	1	8
3001	5	2	—	1	—	—	1	—	1	1	11
3006	5	1	—	—	—	—	1	1	3	—	11
3014	3	4	—	—	—	—	1	—	3	—	11
3015	6	1	—	—	2	—	4	2	4	1	20
3017	7	2	1	—	—	—	3	—	2	—	15
3018	1	1	—	—	—	—	1	—	3	—	6
3020	3	1	—	—	—	—	1	1	—	1	7
3021	—	1	—	—	—	—	1	1	—	1	4
3022	10	1	3	—	—	2	6	—	5	—	27
3025	2	—	—	—	1	—	2	1	1	1	8
TOTAL	45	14	5	1	3	3	22	6	23	6	
Total by Class	59		6		6		28		29		128

stances of premature graying, four were reported among the nine dyslexic members of this family. The significance of this observation is unknown.

Discussion

The families reported here show a pattern of inheritance that is consistent with autosomal dominant inheritance. Because of the mode of ascertainment, as discussed above, proof of this hypothesis awaits either the identification of one or more genetic linkages or gene localizations or the introduction of a specific diagnostic technique which would permit a less biased ascertainment of families. Several conclusions, however, can be drawn from this set of pedigrees that have important implications for understanding the biology of dyslexia and the problems that have influenced both prior genetic studies (Finucci et al. 1976; DeFries 1989) and recent twin studies (DeFries et al. 1991) relating to the inheritance of dyslexia.

From the present data, almost a quarter of adults with a gene leading to dyslexia do not have problems with reading or spelling and do not meet the criteria for dyslexia used in the present study. About half of these, as obligate carriers, had no history or diagnosis of dyslexia, although the other half had either a strong or confirmed history of dyslexia but were presently compensated. This may explain, in part, why positive family histories may not always be obtained in children with dyslexia of "unknown" cause. These observations are important both from the standpoints of counseling families about the risk of future children being affected as well as the obvious importance of the knowledge to families that essentially normal reading ability may be reached by some children, particularly female children. Whether the improved reading ability that occurs in some adults is due to remediation, the development of more effective strategies for reading, or further maturation of the central nervous system, or simply reflects the variation in severity that accompanies most autosomal dominant disorders is not currently clear, but the phenomenon appears to be real. Although a portion of this variation might be explained by other modes of inheritance (major gene or polygenic inheritance), this would not explain the existence of compensated adults. Problems with spelling, difficulty with nonsense passages and tests for non-words (Gross-Glenn et al. 1990; Wood et al. 1991) still remain for the majority of adult dyslexics.

Dyslexic individuals did not differ from normal readers in terms of their educational history, marital stability, or income level. Our results do not support the possibility that left-handedness is more frequent in familial dyslexia. Thus, these data indicate that familial dyslexics are

comparable to their unaffected counterparts on nearly all the variables sampled. We also did not find a higher proportion of males in our dyslexic sample. Preliminary data from the study, however, suggest that the severity of the defect in reading and spelling may be greater in males (Feldman et al. 1993a). The increased severity in males may also provide a partial explanation for the greater frequency in males that has been reported and explain the observation that all six compensated adults in the present study were female.

Family 3017 is of particular interest. The dyslexics differed from other families in having co-occurring ADHD, psychological problems, and in having a superior performance on a word fluency test, as reported previously (Lubs et al. 1991b). The current questionnaire data also suggests an increased frequency of premature graying. The unusual sex ratio (only one of nine dyslexics was male) was probably due to chance. These data suggest genetic heterogeneity, but the small numbers of affected individuals and families does not yet permit adequate statistical evaluation of this possibility.

Handedness, allergy, and autoimmune disease have been analyzed in dyslexics and non-dyslexics using similar historical data in several other recent studies. The present study and that reported by Pennington et al. (1987) were quite similar in design and structure. Both were primarily studies of familial dyslexics and incidentally gathered historical data on these and other medical questions. The study carried out by Hugdahl, Synnevag, and Satz (1990) compared the medical histories of the parents of 105 dyslexic and 105 control children. These were not, however, stated to be cases of familial dyslexia, and no family information was provided. In the Colorado reading project, DeFries et al. (1991) carried out a series of studies in the families of twins, as well as concordance and cross-concordance studies in DZ and MZ twins. Family history of dyslexia was not a factor in the analysis, however.

None of these studies demonstrated an increased frequency of left- (or non-right-) handedness in dyslexics. Only the study by Hugdahl, Synnevag, and Satz showed an increase in allergy in dyslexics and the overall data in these studies does not support a relationship between the allergy and dyslexia. The careful study by Pennington et al. showed an increase in autoimmune disorders in dyslexics (7/70) compared to unaffected family members (1/66). Only medically documented autoimmune disorders were included. When one family in which there were three reports of autoimmune disease was omitted, however, the frequency of the association fell from 10 percent to 7.8 percent and the difference between dyslexics and normals was no longer significant. As discussed by these authors, it is possible that there is a genetic subtype of dyslexia in which there is an association

with autoimmune disease, but this was clearly not observed in the present study (Table IV). The questionnaire data of Hugdahl showed an increased frequency of autoimmune disorders in five of 105 dyslexic children but in no control children. It is possible, since requests for participation were widely circulated, that responses were biased in some fashion. In these four studies, therefore, a variable or weak co-occurrence was found in only two instances. These results clearly do not support either an etiological relationship or consistent association between autoimmunity, handedness, and dyslexia, either familial or undefined, as originally proposed by Geschwind and Behan (1982).

Conclusion

The findings in the current study of eleven three-generation families are consistent with the hypothesis of autosomal dominant inheritance with reduced penetrance. Of the 74 family members determined to have a gene leading to dyslexia, 61 were clearly affected, six were classified as compensated adults (8 percent) and seven as obligate carriers (9 percent). Severity was greater in males and each of the six compensated adults were female. The data do not support an increased frequency of males, left-handedness, or autoimmune disorders in dyslexics and the long-term outcome is comparable in dyslexics and non-dyslexics.

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