# Genetic Studies and Linkage Analysis of Specific Dyslexia: Evaluation of Inheritance in Kindreds Selected for Apparent Autosomal Dominant Transmission

by

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TABLE OF CONTENTS

# VIII. SUMMARY

Specific reading disability is defined as a serious difficulty in learning to read and spell despite adequate intelligence and opportunity, and without demonstrable neurological, sensory, or emotional etiology. This study was designed to investigate the existence of a hereditary form of specific reading disability, or developmental dyslexia, through the use of genetic studies and linkage analysis. The diagnostic effectiveness of a screening battery of tests was evaluated by discriminant analysis, and the resulting classifications were also subjected to segregation and linkage analysis.

Initial diagnosis of dyslexia was based on school and medical history and testing. In school-age children, at least a two-year deficit in reading compared to non-reading abilities was required. Similar criteria were used for adults, with emphasis upon a history of early and specific reading disability. All individuals were at least of average intelligence ($IQ \geq 90$).

Selection of families was designed to provide the optimal population for linkage analysis. Eight Caucasian kindreds including sixteen families were ascertained, and all had at least a three-generation history of dyslexia. In all but two kindreds three generations and/or related sibships were studied. Seventy-three individuals could be tested, and history and school records were utilized for another eleven. Fifty-three individuals were found to be affected.

The pedigrees suggested autosomal dominant inheritance of dyslexia; however, the segregation ratio of 0.76 (32/42) was significantly higher than the 0.50 expected for an autosomal dominant trait ($X_1^2=11.52$, $p<0.001$). The sex ratio of 1.83:1 among affecteds (33 males to 18 females) was also significant ($X_1^2=4.41$, $p<0.05$). This was partially attributed to the

ascertainment design, favoring kindreds with several multiplex sibships to increase the chances of detecting a major gene effect. Bias towards affecteds was especially notable in the selection of related families in kindreds in which the entire parental sibship and their families could not be tested. Ascertainment was also biased in favor of males, as they tended to be more severely affected. All probands were male, and analysis of variance of discriminant scores of 28 affected males and 16 affected females showed a significant difference in test performance ($F=10.45$, $p<0.005$).

Discriminant analysis was based only on tests contributing significantly to the classification (two tests for children, three for adults). All 31 children but only 31 of 42 adults were classified in agreement with the initial diagnosis. Segregation analysis using the discriminant function diagnoses suggested polygenic or recessive inheritance in three families in which affected mothers were re-classified as normal; alternatively, decreased severity in females could have contributed to their misclassification.

Linkage analysis, performed between dyslexia and 23 genotyping markers as well as Q-, C-, and R-banding chromosomal variants, resulted in a lod score of 2.359 at $\theta=0.1$ for dyslexia and chromosome 15 short-arm heteromorphisms when the initial diagnoses were used. No other lod was greater than one. This is somewhat suggestive of linkage and, if confirmed, would best be explained by the existence of a major gene effect upon reading ability; however, because of the possible variability in the phenotyping and observed segregation distortion for these particular markers, a lod score greater than the customary 3.0 should be required to establish the linkage relationship. In addition, linkage analysis using the diagnoses from the discriminant function produced a lod score of 1.836 at $\theta=0.0$ for dyslexia and chromosome 15p, so the decision as to whether dyslexia is an autosomal dominant trait must await further investigation into this relationship.