Using Genetics to Understand Dyslexia

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This paper reviews what is currently known about the genetics of dyslexia and shows how genetic studies can help clarify which symptoms are primary and which are secondary in dyslexia. On the genetic side, current evidence supports the view that dyslexia is familial, substantially heritable, and heterogeneous in its genetic mechanisms. At least some forms of familial dyslexia appear to be autosomal dominant, with linkage studies supporting both a major locus on chromosome 15 and genetic heterogeneity. On the symptom side, current evidence supports the view that the primary symptom in dyslexia is a deficit in the phonological coding of written language. This primary symptom likewise appears to be heritable. Recent evidence suggests that the heritable precursor to this written language deficit is a spoken language deficit in the skill of phoneme segmentation and awareness.

Dyslexia, like other complex behavioral disorders, confronts us with a baffling array of symptoms. There are reported associations between dyslexia and abnormal eye movements, left handedness, letter reversals, attention problems, poor self esteem and depression, juvenile delinquency, early articulation problems, word finding problems, verbal short term memory problems, tic disorders, and even immune disorders. Which of these associations are genuine? Of those that are genuine, which are part of the cause of dyslexia? Obviously not all gen-

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uine symptoms are part of the cause of a disorder. Some are just correlates of the underlying cause and others are a result of the disorder. As long as we stay at the level of symptoms, it is difficult to answer these questions. But answering these questions is important, not only for our scientific understanding of dyslexia, but also for effective diagnosis and treatment. Clearly some treatments for dyslexia are targeted at symptoms that are only artifactually related to the disorder. Effective treatments must address the underlying cause of dyslexia, whether at the level of psychological processes or at the level of biology.

In this paper, I will show how analyses that look below the symptom level, in particular, behavior genetic studies, can help to resolve some of this confusion.

Considerable progress has been made in the last ten years in defining both the genetics and the behavioral phenotype of dyslexia. The pathophysiology of dyslexia below the level of behavior is less well understood, though there is evidence for left hemisphere brain dysfunction. Dyslexia may be simply defined as unexpected difficulty in the acquisition of reading and spelling skills. Generally accepted prevalence rates for dyslexia are 5–10 percent, with a male:female sex ratio of 3.5–4.0:1. The sex ratio in familial samples is considerably lower, about 1.8–2.0:1 (DeFries in press).

Sex differences in rates of a disorder can sometimes provide clues about the biology of a disorder. There are several possible genetic explanations of the sex differences in dyslexia. These include a polygenic model with a lower threshold for males or a major locus model with a sex difference in expressibility. X-linked inheritance does not fit the available family data. Polygenic means that many genes act together in an equal and additive way to produce the trait, whereas a major locus model assumes one or two genes have a major role in producing the disorder. X-linked inheritance refers to a gene carried on the X-chromosome. If the gene is recessive, males will get the disorder much more frequently than females because males have only one X chromosome, whereas females have two.

These prevalence estimates for dyslexia, of course, depend on how the disorder is defined. As is true for other behaviorally-defined disorders, there is disagreement about the diagnostic definition of dyslexia. One of the key themes of this review is how behavior genetic and experimental analyses can help in defining both the phenotypic core and the phenotypic boundaries of a complex developmental disorder like dyslexia (Pennington and Smith 1988).

Converging evidence indicates that dyslexia is a developmental language disorder which mainly affects the phonological domain of language. Heritable differences in particular spoken language skills, especially awareness of phonemic segments in words, lead to problems

in the phonological coding of written language, which is a key prerequisite for skill in single word recognition and spelling. In this review, we will consider some of the evidence that points to this broad conclusion.

Conceptually, genetic analyses proceed in a series of linked steps considering in turn the questions of *familiality, heritability, mode of transmission,* and *gene locations.* The first part of the review will be organized accordingly. Then we will consider the issues of *heterogeneity* and *behavioral phenotype.*

Familiality refers to whether the disorder runs in families. Familiality is measured by comparing the rate of the disorder in relatives of an affected person to the baseline rate found in the general population. Although familiality is generally necessary for indicating genetic influence, it is not sufficient to establish genetic influence, since behavioral traits can obviously run in families for environmental reasons. For instance, bad table manners are likely familial but unlikely to be genetic. *Heritability* refers to what proportion of the variation in a trait is due to genetic influences. Knowing that a trait is heritable, at least in part, does not tell us how it is inherited—what the *mode of genetic transmission* is. As discussed above, genetic transmission can be polygenic, due to a major locus, or X-linked, to name some of the more common modes of transmission. More complex modes are possible, including the mixed model in which a major locus interacts with a polygenic background for the trait. Knowing the mode of transmission does not tell us *gene locations.* To answer this question, we must perform linkage analysis, in which the cotransmission of a trait and genetic markers provides information about the location of genes affecting the trait. There may be several different genetic mechanisms that can lead to the same trait; this situation is termed *genetic heterogeneity.* Finally, the term *behavioral phenotype* refers to the expression of a gene or genes for a trait at the level of behavior. One of the key questions we are concerned with here is which of the many symptoms found in dyslexia are actually part of its behavioral phenotype.

Familiality. Familial aggregation in dyslexia was soon noticed after the disorder was first described by Kerr (1897) and Morgan (1896). It was reported in a number of case studies (Fisher 1905; Hinshelwood 1907, 1911; Stephenson 1907; Thomas 1905) that children with dyslexia often had affected relatives. Of these, Thomas' (1905) report of two affected brothers and another child with an affected sister and mother was the first to note the familial tendency in dyslexia. Stephenson (1907) reported a three-generation family history affecting five females and one male. These early reports documented a number of aspects of the clinical presentation of dyslexia which have been substantiated by subsequent research: early manifestations often include difficulty in

learning letter names; affecteds are frequently good at mathematics and spatial tasks; severity varies across affecteds; and the deficit persists into adulthood, either as a problem with both reading and spelling or just spelling.

The magnitude of familial risk for dyslexia has not been measured in a representative population sample until recently. In a selected sample of families, Hallgren (1950) had found the risk to first degree relatives to be 41 percent, which is considerably higher than the population risk (5–10 percent). However, Hallgren's (1950) diagnoses of affected family members were not based on testing, and ascertainment biases may have led to the selection of families with higher than normal proportions of affected relatives. Vogler, DeFries, and Decker (1985) measured familial risk for dyslexia in the Colorado Family Reading Study (CFRS) sample, which was a representative population sample, and found the risk to a son of having an affected father is 40 percent and of having an affected mother 35 percent, a five-to-seven-fold increase in risk over that found in sons without affected parents. For daughters, the risk for dyslexia of having an affected parent of either sex was 17–18 percent, a ten-to-twelve-fold increase over that found in daughters without affected parents. These risk figures are somewhat lower than Hallgren's (1950), but still substantially elevated, and clearly demonstrate familiality.

Similar estimates of familial risk (range 36–45 percent) have also been reported by Klasen (1968), Naidoo (1972), Zahalkova, Vrzal, and Kloboukova (1972), and Finucci et al. (1976). The magnitude of familial risk for dyslexia is clinically significant in that family history could be used to help screen for children at high risk for this disorder.

Heritability. The next question to consider is whether this familiality indicates genetic transmission. Twin studies have been mainly used to address this question in dyslexia. Earlier twin studies, which indicated substantial heritability of dyslexia, had methodological problems, such as biases of ascertainment, failure to limit the dyzogotic (DZ) twin comparison group to same sex twins, and lack of objective diagnostic criteria. Two well-designed twin studies have recently been conducted which avoided these methodological problems.

One study (Stevenson et al. 1986) examined a large population cohort of adolescent twins in London, only some of whom (naturally) were dyslexic. The authors tested for the heritability of both reading and spelling skill in the whole population, as well as specific reading and spelling retardation in a subset of the population. They found only modest heritability for reading ability and disability, but significant heritability for spelling ability and disability. Their results for reading are discrepant from all other twin studies and may be due to the older age of their sample.

The second study was conducted by John DeFries and colleagues at the Institute for Behavior Genetics in Boulder (1987). They have developed a new, multiple regression technique for testing heritable and common environmental contributions to extreme low scores on a continuous trait in a twin study. This method assumes that at least one twin in each MZ or DZ pair is disabled, as do traditional twin studies. But instead of examining differential (categorical) concordance rates, this technique examines differential regression to the population mean in the co-twin, thus making full use of the information available in a continuous variable, like reading scores. To the degree that the condition is heritable, there should be greater regression to the mean in the DZ co-twin scores (because their degree of relationship is .50, whereas that in MZ twins is 1.00). An expanded version of this model (LaBuda, DeFries, and Fulker, 1986) can estimate both heritability and shared environmental influences. With a large enough data set, this model can also test for major gene effects.

These investigators used this technique to test for the heritability of reading, spelling, and related cognitive skills in a sample of 64 MZ and 55 DZ twins, in which at least one member of each pair was reading disabled (DeFries, Fulker and LaBuda, 1987). Significant heritability was found for PIAT Reading Recognition, PIAT Spelling, and WISC-R Digit Span, whereas it was not found for PIAT Reading Comprehension, WISC-R Coding, or the Colorado Perceptual Speed test. The estimate of heritability for a composite discriminant score was 0.29, suggesting about 30 percent of the cognitive phenotype in reading disability is attributable to heritable factors. It is important to note that this result was not simply due to the heritability of IQ, since IQ was controlled in these analyses.

The pattern of scores across different measures in this study begins to provide information about which components of reading are genetically influenced in dyslexia. Single word reading and spelling in dyslexia were found to be genetically influenced independent of IQ, but reading comprehension was not. In the area of reading-related skills, a measure of verbal short term memory (Digit Span) was found to be genetically influenced, but measures of perceptual and motor speed were not. These results fit with a growing consensus that dyslexics are more deficient in single word recognition skills than in comprehension skills and that the precursor to this deficit in single word reading is in the domain of phonological processing skills.

Olson et al. (in press) analyzed the heritability of phonological versus orthographic coding in single word reading in the dyslexic twin sample studied by DeFries, Fulker, and LaBuda (1987). Quite strikingly, Olson et al. (in press) found significant heritability (about .46) for a phonological coding measure (i.e. oral nonword reading accuracy).

In contrast, a measure of orthographic coding skill in single word reading was not found to be heritable. Moreover, the contribution of phonological coding to the heritability of reading in these twins was .93 ± .39, whereas the contribution of orthographic coding was essentially zero. Other evidence argues against problems in orthographic coding being a causal deficit in dyslexia (Olson 1985; Pennington et al. 1986), whereas the evidence supporting a deficit role for phonological coding is strong. Thus it is quite interesting that the deficient component is likewise the heritable component.

The next key question of interest is which phonological processing skills at the level of spoken language are a heritable precursor to this heritable deficit in the phonological coding of written language. Olson et al. (in press) found significant ($p < .05$) heritability estimates for the correlation between two different phoneme awareness measures, rhyming fluency ($h2 = .99 \pm .86$) and Pig Latin ($h2 = .81 \pm .75$) and the heritable nonword reading measure. These investigators pointed out that the large confidence intervals on these estimates meant these results need to be confirmed by future studies. Nonetheless the pattern of results is consistent with the overall argument we have been developing here. We expect that the heterogeneous etiologies that lead to dyslexia don't affect reading directly, but instead alter the development of spoken language skills important for later reading development. These behavior genetic analyses are consistent with the view that the heritable component in dyslexia at the written language level is in phonological coding and the heritable precursor to this deficit in phonological coding is a deficit in phoneme awareness.

Modes of transmission. While twin or adoption studies are informative about the presence of genetic influences, they do not ordinarily address the issue of the mode(s) of genetic transmission. A number of different modes of transmission have been proposed in dyslexia, including autosomal dominant transmission (Hallgren 1950; Zahalkova, Vrzal, and Kloboukova 1972), but there has been really only one modern complex segregation analysis performed on this disorder (Lewitter, DeFries, and Elston 1980).

This study included 133 nuclear families, all members of which were tested. Rather than a discrete phenotype definition, a continuous phenotype measure based on a discriminant analysis was employed. A shortcoming of this study is that adults with a positive history of dyslexia but normal test scores (compensated adults) were not counted as affected.

In the population as a whole, no support was found for a single major locus (autosomal dominant, autosomal recessive, or codominant transmission), but the null hypothesis of no vertical transmission was likewise rejected. These investigators also tested different models of

transmission in subpopulations, including families with probands of a given sex, families with severely affected probands, and children considered alone, because of possible unreliability of the measures in adults. Autosomal recessive inheritance could not be rejected in families with female probands, and codominant inheritance was supported when children were considered alone. The authors concluded that their results likely indicated genetic heterogeneity. This conclusion is similar to that reached by Finucci et al. (1976) in a well-conducted study of 20 extended families, all members of which were tested. Unfortunately, this sample was too small to permit a formal, complex segregation analysis.

In short, the existing data support genetic heterogeneity in the transmission of dyslexia, but do not converge on which different modes of transmission are operating. There is clearly a need for more data on this issue, especially a segregation analysis of a large sample of dyslexic families which employs several different phenotype definitions (including compensated adults) and which uses a more sophisticated segregation analysis program, such as POINTER (Lalouel et al. 1983).

Gene locations. We have been conducting linkage studies of dyslexia for about ten years now, and the main results are (1) significant evidence for linkage between dyslexia and chromosome 15 heteromorphisms in a minority of families with apparent autosomal dominant transmission (Smith et al. 1983), and (2) significant evidence of genetic heterogeneity (Smith et al. in press). We are currently testing the linkage to chromosome 15 with DNA polymorphisms in the same region as the original marker, and we are looking for a possible second dyslexia locus on another chromosome in the majority of families who are not linked to chromosome 15. A clue about where to look for a second locus has been provided by the association we and others have found between dyslexia and immune disorders (Geschwind and Behan 1982, Pennington et al. 1987). We are currently testing for a possible second locus on chromosome 6 near the HLA region.

In the original study (Smith et al. 1983), which found significant linkage between dyslexia and chromosome 15 heteromorphisms, there was one family which had substantial negative LOD scores for markers on chromosome 15, arguing against linkage in that family (A LOD score is a logarithm of the probability of X linkage). However, a test for heterogeneity was not significant. Since then we have doubled the number of families in the sample and more than doubled the N. We now have linkage data on 245 individuals in 21 extended families. When we tested this larger sample for genetic heterogeneity using Ott's (1985) HOMOG program, the hypothesis of heterogeneity was supported over two competing hypotheses: That of homogeneity and

that of no linkage (Smith et al. in press). HOMOG estimated that dyslexia is linked to chromosome 15 in about 20 percent of the families. The range of LOD scores in the entire sample of families spans six orders of magnitude, from negative LOD scores less than −3.0 (i.e., 1000:1 odd against linkage to 15) to a positive LOD score of 3.2 (i.e., 1000:1 odd in favor of linkage to 15), which by itself indicates linkage to chromosome 15 in one family.

A Danish study (Bisgaard et al. 1987) failed to find linkage between dyslexia and chromosome 15 heteromorphisms. Since only five families were studied, this apparent nonreplication may only be due to heterogeneity (since dyslexic families linked to 15 appear to be rarer than those not so linked). In addition, there were other problems with this study. Only nuclear families were studied and the diagnosis of dyslexia was based on questionnaire rather that test data. However, confirmation of our original linkage results by both different investigators and by different markers on chromosome 15 is obviously important.

The results of the linkage work on dyslexia is similar to the results emerging from linkage studies of other complex behavioral disorders, including schizophrenia, bipolar illness, and Alzheimer's disease. That is, there is evidence for both linkage and genetic heterogeneity. What is currently unclear is how common are the single major locus forms of these disorders. Nonetheless, it is certainly true that single gene effects are turning out to be more important in understanding complex behavioral disorders than was previously thought.

Heterogeneity. Both the results of segregation and linkage analyses support the not too surprising conclusion that dyslexia is genetically heterogeneous. Additional support for this conclusion is provided by the finding of high rate of dyslexia among boys with a 47, XXY karyotype (Pennington et al. 1982); this sex chromosome anomaly is too rare (about 1/1000 male births) to account for much of the genetic influence on dyslexia.

But heterogeneity in etiology does not necessarily indicate heterogeneity in pathophysiology; there may not be a 1:1 mapping between etiologic and phenotypic subtypes. In fact, the evidence for discrete phenotypic subtypes in developmental dyslexia is much less compelling than it once appeared. Current evidence supports the view that the vast majority of developmental dyslexics have an underlying problem in the phonological coding of written language. While there are individual differences in this and other component reading processes within the dyslexic population, there is little evidence for discrete subgroups (Olson 1985).

Thus, at the level of behavior, the final common pathway in most of developmental dyslexia is a deficit in phonological coding. We know virtually nothing about the role of biochemistry in the pathophysiol-

ogy of dyslexia. More is known about neuroanatomy and neurophysiology, although much remains to be known. The general consensus is that dyslexia involves dysfunction in the left cerebral hemisphere (Galaburda et al. 1985). The more interesting question of how a developmental disorder affecting the left hemisphere largely spares conversational speech and language has hardly been addressed.

Behavioral phenotype. There has been considerable progress within the last ten years or so in defining the behavioral phenotype in developmental dyslexia. The work of Vellutino (1979) and others established clearly that the main deficit in most developmental dyslexics is linguistic rather than visual. As discussed above, more recent work has shown that within the linguistic domain, it is the phonological level of language that is critically affected. For conceptual clarity, we divide these phonological problems into those that involve spoken language skills (such as phonemic segmentation) and those that involve written language (such as nonword reading). We have presented some of the evidence for the view that the spoken language precursor to the phonological coding deficit in written language is a deficit in phonemic segmentation and awareness skills; other relevant articles include Bradley and Bryant (1978, 1983); Pratt and Brady (1988); and Wagner and Torgesen (1987). Reading experience also facilitates phoneme awareness (Morais et al. 1979). Thus, the relationship between reading skill and phoneme awareness appears to be one of reciprocal causation.

The phenotypic core of dyslexia is becoming well defined, but we are less certain about phenotypic boundaries. Dyslexics have other problems with phonological processing in spoken language, such as problems with speech production (Catts 1986, 1988), name retrieval (Katz 1986), and verbal short term memory (Jorm 1983; Stanovich 1982a, 1982b). What is unclear at this point is what is the causal relation of these other phonological processing problems to dyslexia. Are they other manifestations of the underlying cause, correlates of the underlying cause, a result of poor reading, or just incidental to the syndrome?

Recent results from our laboratory (Pennington et al. in press) and from others (Conners and Olson in press; Mann and Dituno in press) support the view that these various phonological processing skills are not a unitary domain nor do they all have a similar causal relation to reading skill. In these studies, measures of phoneme awareness loaded on a separate factor from measures of verbal STM and accounted for much more unique variance in reading skill. Thus it appears that the deficits in verbal STM often found in dyslexic populations are more likely to be a correlate or a result of reading problems than a cause, whereas the evidence for a causal relation for problems in phoneme awareness is fairly strong.

Similar questions about the causal relation to dyslexia exist for characteristics more distant from the phenotypic core, such as left handedness, attention problems, and problems with self-esteem and depression. There is also an association between dyslexia and immune disorders (Geschwind and Behan 1982); Pennington et al. 1987), the basis for which is not well understood. How do we interpret this evidence for comorbidity in dyslexia? It seems likely that problems with self-esteem and depression are a result of dyslexia. Since left-handedness and attention problems are not found in every dyslexic sample, these symptoms may have an incidental or artifactual relation to dyslexia. But we really lack good data on these questions.

The techniques of behavior genetics can help to answer these questions about phenotype boundaries, just as they have helped to define the phenotypic core. For instance, coheritability analyses can address the issue of whether an associated symptom is causally or artifactually related to the phenotype of dyslexia. Pauls et al. (1986) have used these analyses to clarify which associated symptoms are part of the phenotype in Tourette syndrome, (chronic tics and obsessive compulsive disorder appear to be) and which are not (attention problems don't appear to be).

A final issue of considerable interest for genetic studies is whether there exists a subclinical marker for dyslexia. Since some adults compensate for their earlier dyslexia, do they nonetheless have persisting behavioral characteristics could be used to validate a diagnosis based on history? This is an important question for behavior genetic studies in which there is a need to diagnose adult family members. What little research there is suggests that problems in phonological coding and phoneme awareness are among the most persistent features of the disorder (Campbell and Butterworth 1985), but more work is needed to see whether such problems will be useful as subclinical markers.

Summary. The behavior genetic analyses we have just discussed allow us to make some sense out of the welter of symptoms associated with dyslexia. The underlying neuropsychological deficit in dyslexia appears to be a problem in phoneme segmentation or phoneme awareness skills which causes the primary symptom in dyslexia, a deficit in the phonological coding of written language. There is converging evidence that both of these symptoms are genetically influenced. The deficit in phonological coding, in turn, causes the other problems dyslexics have with reading and spelling, including letter reversals, slow reading rate, dysfluent oral reading, poor reading comprehension, and abnormal eye movements during reading. More distant secondary symptoms probably include problems with self esteem and depression, and in some populations, delinquency as well. Other spoken language problems, such as word finding problems and verbal short term

memory problems, may be related to the underlying phonological cause, but do not appear to be as important as the deficit in phoneme segmentation skill in causing dyslexia. These other spoken language problems may also partly be a result of dyslexia. We have already said that the relation between dyslexia and attention problems and left-handedness appears to be incidental. The association with immune disorders may be genuine, but more data are needed to tell us what this association means.

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