Genetic Influences on Learning Disabilities and Speech and Language Disorders

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Pennington, Bruce F., and Smith, Shelley D. Genetic Influences on Learning Disabilities and Speech and Language Disorders. CHILD DEVELOPMENT, 1983, 54, 369–387. This paper is a comprehensive review of known examples of genetically influenced learning disabilities (LDs) and speech and language disorders (SLDs). The review is divided between 2 broad classes of studies: (a) those which begin with an LD or SLD phenotype that appears to be familial and attempt to learn more about the specifics of genetic transmission, if any; and (b) those which begin with a group of individuals, all of whom share a given documented genetic risk factor, to see if it leads to a specific LD or SLD. Included in the first category are familial dyslexia, stuttering, and other speech and language disorders. In the second category are included sex chromosome anomalies, treated PKU, and minor autosomal anomalies. Issues of definition, variability, and developmental changes in the cognitive phenotype are discussed throughout. The implications of this work for our understanding of cognitive development and its bases in brain development and genetics are also discussed.

Introduction

Although learning disabilities (LDs) are the most common handicapping condition of childhood (with an estimated incidence of 15% or greater), relatively little is known about their etiology. The large majority of LD children seen clinically cannot be clearly assigned an etiology, even when they receive an extensive interdisciplinary evaluation. In the absence of a clear understanding of etiology, it is difficult to approach early detection, prevention, intervention, or prognosis in a rational way. It is increasingly recognized that LDs are quite heterogeneous both in their etiology and in their clinical presentation and course (Benton & Pearl, 1978; Rie & Rie, 1980). A number of environmental factors significantly increase the risk for LDs, including prenatal exposure to alcohol, perinatal complications, postnatal exposure to lead (Needleman, 1980), and decreased parental and environmental stimulation. Similar considerations hold for speech and language disorders (SLDs). The purpose of this paper is to discuss what is known about genetic influences on LDs and SLDs and to suggest avenues for future research.

Before proceeding to review specific studies of genetic influences on LDs and SLDs, it is important to consider some of the theoretical issues involved in applying genetic models to the understanding of these disorders. It is also important to appreciate that genetic factors can cause subtle changes in cognitive development, as well as the more familiar obvious changes found in cases of genetically caused mental retardation.

The general approach taken to resolve some of the heterogeneity of mental retardation into genetically homogeneous subtypes (e.g., Penrose, 1938) can be profitably applied to LDs (see Childs & Finucci, 1979; McClearn, 1978; Omenn, 1973; Vandenberg, 1973). In the case of mental retardation, the retarded portion of the population distribution of general intelligence proved to have two
different components. One was simply the tail of the normal distribution and the other was a separate, smaller distribution with a markedly depressed mean. While both distributions were genetically influenced, the second distribution reflected pathologically different etiologic factors in the development of overall abilities and was eventually resolved into a number of pure genetic and acquired subtypes.

On the genetic side, it turned out that there were several different genetic mechanisms that could cause mental retardation, including polygenic inheritance, major genes, and chromosome alterations. Each of these mechanisms, which are explained below, are also involved in the etiology of some LDs and SLDs.

If we think of LDs and SLDs as reflecting a depression in specific cognitive skills within a population of individuals all of whom have normal overall IQs, we can apply this same distributional analysis to understanding them. That is, some LDs and SLDs represent the tail of the normal distribution of a specific cognitive or linguistic trait (e.g., verbal processing ability) necessary for one or more academic skills or normal speech and language development. If the specific trait in question shows significant genetic variance, then LDs or SLDs involving that trait can be said to be genetically influenced. Put more simply, the genetic basis of some LDs and SLDs is simply a corollary of the fact that most specific intellectual abilities show both a surprisingly high degree of individual variability and a substantial degree of heritability (DeFries, 1980; DeFries, Vandenberg, & McClearn, 1976).

The genetic model involved in the above discussion is the “polygenetic threshold” model, which assumes that there are a very large number of genes which contribute in an equal and additive fashion to the specific trait in question, and that there is a threshold point beyond which the phenotype in question is expressed (Wright, 1934). In addition to the genetic effects, environmental factors can act to shift the genetic liability distribution, thus influencing the position of a given genotype with respect to the threshold (Carter, 1969; Falconer, 1960). This interaction of polygenic threshold inheritance with environmental influences is termed the multifactorial model. As will be discussed below, there is evidence that this model holds for some forms of reading disability; we will concentrate on the genetic aspects.

In the polygenic case, the threshold of an LD or SLD caused by a low level of a particular cognitive or linguistic ability is somewhat arbitrary, depending both on the expectations in a given academic environment and on how crucial that particular cognitive ability is for a given academic skill. For instance, since language abilities are probably more intimately involved in reading development than are spatial abilities, the threshold point beyond which a reading disability occurs probably differs between these two cognitive ability clusters (see Figure 1). This simple model would help explain why the auditory-verbal subtype of dyslexia has a much higher incidence than the visuo-spatial subtype (Ingram, Mason, & Blackburn, 1970; Mattis, French, & Rapin, 1975). Similarly, if there is a sex difference for the specific cognitive ability involved, then the incidence of the LD in question would differ for each sex. This likely helps explain the 3–5:1 ratio of males to females in reading disability. (Notice that an opposite-sex difference for spatial abilities would not so greatly increase the female incidence of reading disability because of the more extreme threshold point.)

Two other simple genetic models may apply to LDs. Both involve variance which is due to pathological genetic factors that have a low frequency in the general population. One is the two-allele autosomal locus model, which predicts the distribution of genotypes involving a major dominant or recessive gene. The other is simply the bimodal distribution in a given specific cognitive trait caused by the presence of non-Mendelian genetic factors (i.e., chromosomal alterations). These models are illustrated in Figure 2. Both models would cause a “bump” on the lower tail of the normal distribution of a given specific cognitive or linguistic trait and would be analogous to the second type of mental retardation discussed above. What is important to point out is that each of these two models would most likely interact with the polygenic background for the trait in question. Thus, there could be unexpected unequal sex ratios for an LD or SLD due mainly to an autosomal locus, if there was a sex difference in the polygenic background for the underlying trait relevant to that disability. Moreover, among affected individuals of the same sex, there could also be phenotypic variability due to interactions between the major gene and the remainder of the individual’s genome. Examples of both of these kinds of effects in specific genetic LDs and SLDs will be pre-
Normal Distributions of Verbal (A) and Spatial (B) Skills

A

Reading Disabled

B

Reading Disabled

Distribution of Verbal Abilities by Sex

Fig. 1.—Sex differences in cognitive skills and the incidence of polygenic reading disability

1. Two Allele, Autosomal Recessive

Threshold

Homozygous Abnormal
Heterozygous
Homozygous Normal

2. Two Allele, Autosomal Dominant

Threshold

Homozygous Abnormal
Heterozygous Abnormal
Homozygous Normal

3. Bi-Modality Due to Non-Mendelian Genetic Factors

Threshold

Fig. 2.—Models of three types of major genetic influences
sented below. The model which incorporates these kinds of interactions is called a mixed model; a mixed model which assumes a two-allele, single autosomal locus with polygenic background has been developed (Morton, Yee, & Lew, 1971). This kind of model is probably most appropriate for the genetic analysis of complex behavioral traits such as LDs and SLDs.

We have discussed the three basic genetic mechanisms or models that can be applied to LDs and SLDs, and have stressed how both major genes and chromosome alterations could interact with the polygenic background to produce unexpected sex ratios and phenotypic variability.

Two different general approaches may be taken in attempting to identify genetically influenced LDs and SLDs. The first, and by far most common, is to identify an LD or SLD which gives evidence of familiality and then to identify a subtype (or subtypes) which is consistent within families. The second, and much rarer, approach is to identify a population all of whom share a common genetic risk factor (such as a sex-chromosome anomaly) and then see how many of them develop LDs or SLDs. Specific examples of both approaches will be presented below. A continuing theme in both approaches is the challenge of deciding when two individuals have the same phenotype, even when they share the same genetic alteration, since an LD or SLD represents a complex cognitive or linguistic phenotype which changes with development and which is modified by a host of environmental factors.

Review of Studies of LDs and SLDs That Appear Familial

Dyslexia.—Dyslexia may be defined as unexpected difficulty in the development of reading and spelling; that is, difficulty in these areas which occurs in the absence of lowered general intelligence, socioeconomic disadvantage, emotional disturbance, documented neurological impairment, or peripheral sensory handicap. The incidence of dyslexia among school-age children has been estimated at 10%, with a sex ratio of between 3-4:1 of males to females. The incidence of familial dyslexia has not been reliably measured. Given these exclusionary criteria, the criteria for dyslexia remain somewhat problematic and vary across investigators, both in the level of impairment required and in the specificity of the impairment to reading and spelling (e.g., do children who also have either arithmetic, handwriting, mild speech, and/or language deficits meet the criteria?). Despite these definitional difficulties, dyslexia has been a well-documented clinical entity for a long time.

Dyslexia was first described by Kerr (1897) and Morgan (1896) and given the name "congenital word blindness." It was soon 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’s (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 a 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. These investigators also postulated that dyslexia was caused by a congenital defect in the angular gyrus of the left hemisphere, which neuro-pathological studies had shown to be frequently involved in cases of acquired alexia in adults. However, the neurological basis of developmental dyslexia still remains unclear and controversial.

Further evidence of heritability has been provided by twin studies in which one or both members of a twin pair were diagnosed as dyslexic (Bakwin, 1973; Hallgren, 1950; Hermann & Norrie, 1958). Comparison of monozygotic (MZ) and dizygotic (DZ) twin pairs offers a unique method for separation of genetic and environmental influences: MZ twins are virtually identical genetically, while DZ twins are no more alike genetically than siblings. The effects of environment within a twin pair are assumed to be the same for both types of twins (see Fuller & Thompson, 1978, for a review of this point). Thus, differences between DZ twins are due to genetic and environmental influences, while differences between MZ twins are primarily environmental in origin. If a trait is genetically influenced, MZ twins are expected to show a significantly higher concordance rate than DZ twins. If a trait is totally genetically determined, the expected concordance rate for MZ twins would be 100%,
and 50% for DZ twins; smaller concordance rates indicate environmental effects. When the above twin studies on dyslexia are combined, there are a total of 43 MZ pairs, 30 (91%) of which were concordant for dyslexia, whereas only 20 (31%) out of 64 DZ pairs were concordant. These data provide evidence of heritability of dyslexia, while also providing some evidence for environmental influence. A criticism of these studies is that they did not always report whether the DZ twin pairs were of the same sex. If they were not, that creates a problem because of the overall sex difference in the incidence of dyslexia. Interestingly, Bakwin (1973) found a lower sex ratio (1.64:1) among his dyslexic twins than is reported for the general population, suggesting that, in samples with high evidence of heritability, the incidence for males and females may be more nearly equal.

A second type of twin study, which involves measures of reading achievement in larger, normal samples of child and adult twins, provides consistent evidence of significant genetic variance in normal reading ability. Matheny and Dolan (1974) presented such a study in children and reviewed four studies of adult and adolescent twins, all of which found significant evidence of greater similarity among MZ than DZ twins on various reading measures.

There have been a number of family studies of dyslexia. Such studies have the advantages of (a) providing more detailed pedigrees than do clinical reports; (b) giving information about the adult phenotype and suggesting developmental changes; (c) identifying subtypes of dyslexia; and, in some cases, (d) testing specific genetic models of transmission. Genetic influence upon a trait can be supported by demonstration of expected correlations between relatives or expected segregation in appropriately ascertained sibships. Environmental influences are not controlled, however, so that a fit with a genetic model (often without existence of a corresponding environmental model) still cannot be considered as proof of genetic determination. Other studies which show similarities between family members without regard to specific modes of inheritance are interesting, but there is not space to review all of these studies in detail. Both Finucci (1978) and Herschel (1978) have also reviewed the genetics of dyslexia. Several generalizations seem warranted from these family studies.

1. There is strong evidence for familial transmission, in that both siblings and parents of dyslexic probands are significantly lower on reading and some other tests than are control siblings and parents.

2. The sex ratio is greater (3.3–4.1:1) in studies which included most dyslexic or LD children in a school district (i.e., the Colorado Family Reading Study or the study of Owen, Adams, Forrest, Stolz, & Fisher, 1971) than in studies which only included probands with a definite family history (i.e., Omenn & Weber, 1978; Smith, Kimberling, Pennington, & Lubs, Note 1). The sex ratios in these two studies were 1.4:1 and 1.9:1, respectively.

3. Several subtypes of dyslexia were found, corresponding roughly to the subtypes identified in the general reading disability literature (e.g., a visuo-spatial subtype, an auditory verbal subtype, and a mixed subtype).

4. Owen et al.'s (1971) PIQ > VIQ subtype, Omenn and Weber's (1978) auditory and visual subtypes, and Decker and DeFries's (1981) relatively specific reading-disabled subtype all showed evidence of consistency within families (the last only in children), whereas other subtypes identified by each of these investigators did not.

5. Those subtypes which show greatest evidence of familial transmission may account for between roughly 25%–50% of the total dyslexic population.

6. Several aspects of the dyslexia phenotype persist into adulthood, most notably spelling difficulties (Rawson, 1968).

The Colorado Family Reading Study (Decker & DeFries, 1980, 1981; DeFries & Decker, 1981; DeFries, Singer, Foch, & Lewitter, 1978; Foch, DeFries, McClern, & Singer, 1977; Lewitter, DeFries, & Elston, 1980) is worth special note here both because of its size and its methodological sophistication. The study involved 125 reading-disabled children and their immediate families matched with 125 control children and their families (total N = 1,044). All subjects were given a battery of reading and other cognitive tests, the age-adjusted scores from which were reduced to three factors: reading, spatial/reasoning, and coding/speed. Dyslexic children differed significantly from control children on all three factors, and their siblings and parents were significantly lower than control siblings and parents on all but the spatial/reasoning factor. These results provide strong evidence for the familial nature of dyslexia. Individual factor scores were
used to identify four dyslexia subtypes in probands: a spatial/reasoning deficit (23%); a coding/speed deficit (18%); a relatively specific reading-disabled subtype (41%), with a deficit only in reading; and a mixed or global subtype (9%), with deficits on all three factors. These subtypes accounted for 91% of the sample. It is difficult to say whether the relatively specific reading-disabled subtype found by these researchers has been found by other investigators (Boder, 1973; Ingram et al., 1970; Mattis et al., 1975) who have identified subtypes in clinical populations, but a similar subtype was discussed by Hughes and Denckla (1978) as “dyslexia-pure” and mentioned by Satz and Morris (1980) as an “unexpected” subtype, comprising 13% of their sample of reading-disabled children.

Only the relatively specific reading-disabled subtype showed a significant concordance between probands and other family members, specifically siblings. Thus, this subtype gives the strongest evidence of heritability, though the absence of concordance between probands and parents is puzzling, particularly since age-adjusted scores were used. It may be that factor scores obscure cross-generational similarity in more specific cognitive skills intimately involved in reading and spelling. Another criticism of this study is that it did not consider possible developmental changes in the cognitive phenotype, which could easily complicate the search for familial similarity.

Segregation analyses of large numbers of pedigrees have been performed by Hallgren (1950) on 112 two-generation families and by Lewitter et al. (1980) on the 125 two-generation families in the Colorado Family Reading Study. Hallgren (1950) found that 90 of his cases had families with one affected parent and one or more affected siblings. Twelve of his cases appeared to be nonfamilial (no affected relatives) and 10 had both parents affected, as well as affected siblings and, in some cases, other relatives. Across his whole sample, there was a sex ratio of 3.3:1 in probands and 1.2:1 in both siblings and parents, with an overall sex ratio of 1.8:1. The sex ratio for probands is similar to that observed in other clinical samples of dyslexics, whereas that for siblings and parents is similar to that found in other familial samples. Hallgren used the data in the group of 90 families with one affected parent and one or more affected siblings to calculate Mendelian ratios of the proportions of affecteds among all offspring. He concluded that these ratios were consistent with an autosomal dominant mode of inheritance. He also ruled out X-linked inheritance because he found transmission from either parent to both sons and daughters, whereas a X-linked character would not show any father-son transmission. Hallgren’s (1950) study has been criticized because of his reliance on history for diagnosis; his tendency to exclude other, nongenetic etiologic factors which may have been operative in his families; and, most important, his failure to consider the possibility of genetic heterogeneity among the 90 families on whom he performed segregation analyses (see Finucci, 1978), especially since a single gene model did not fit the pedigrees of his female probands (see Foch et al., 1977). Nonetheless, Hallgren’s data provide strong evidence of familial transmission of dyslexia and suggest that one mode of inheritance operative in this complex disorder may be an autosomal dominant one, especially in families with male probands.

The segregation analyses performed on the Colorado Family Reading Study data (DeFries & Decker, 1981; Lewitter et al., 1980) included: (a) tests of sex linkage; (b) a test for increased incidence among relatives of female probands, which increase would be consistent with polygenic inheritance (see Carter, 1975); and (c) use of a computer program (GENSEG), which provided for analysis of a continuous phenotypic measure, to test for autosomal single-locus, two-allele segregation, either dominant or recessive. They found (a) no evidence of sex linkage, (b) evidence consistent with polygenic inheritance, and (c) evidence for genetic heterogeneity, with only the data for female probands supporting autosomal recessive inheritance. No clear mode of transmission was identified for the sample as a whole or for male probands only, suggesting genetic heterogeneity in both these groups. A pedigree analysis of 20 affected families performed by Finucci, Guthrie, Childs, Abbey, and Childs (1976) also supported genetic heterogeneity.

In summary, pedigree and segregation analyses indicate that the genetic mode of transmission of dyslexia is heterogeneous. There is evidence for polygenic inheritance, autosomal dominant inheritance, and autosomal recessive inheritance in female probands. There is no evidence thus far for sex-linked inheritance, though it is clear that there are sex differences in incidence and expressivity.
A more direct test of the mode of inheritance in dyslexia can be provided by a linkage analysis. Genetic linkage is the deviation from Mendel's law of independent assortment of genes and results when two genes are located close together on the same chromosome such that crossing over between them during meiosis is reduced. Thus "linkage" here refers quite literally to two genes being physically linked because they are close together on the same chromosome. Two genes which are linked tend to "travel together" across generations, whereas genes which are not linked are constantly reshuffled. The phenomenon of linkage provides a method of localizing a gene, that is, by seeing if it is linked to a gene whose locus is known. Linkage is measured by the "lod score," or logarithm of odds of likelihood that a given deviation from random assortment of two genes could be found fortuitously. Lod scores from individual families are summed until linkage is refuted with a lod score less than -2.0 or accepted with a score greater than 3.0. Classical linkage analysis involved two traits both known to be genetic. More recently linkage analysis has been applied to behavioral traits with evidence of heritability, such as schizophrenia and alcoholism (e.g., Elston, Kringlen, & Namboodiri, 1973; Winokur, Tanna, Elston, & Go, 1976). A linkage analysis is only appropriate for a trait expected to be due to major gene inheritance; a polygenic trait obviously would not give evidence of linkage to a particular locus. Therefore, in a genetically heterogeneous condition such as dyslexia, it would be important to identify a subsample of affected families whose pedigrees are all consistent with a particular type of major gene inheritance.

In the Genetics of Specific Dyslexia Project (Pennington, McCabe, Smith, Kimberling, & Lubs, Note 2; Smith, Kimberling, & Lubs, Note 3; Smith et al., Note 1; Smith, Pennington, Kimberling, & Lubs, Note 4; Smith, Pennington, Kimberling, & Lubs, Note 5), the assumption was made that one form of familial dyslexia is inherited in an autosomal dominant fashion. Families with a three-generation history of specific reading disability were solicited from specialized schools or parents' groups. If the pedigree was consistent with autosomal dominant inheritance, all family members over 8 years of age were given a battery of achievement tests. Diagnosis of reading disability in childhood was based on a history of early difficulty learning to read and spell and an oral reading level 2 years below their other academic skills. Since adults may have compensated for earlier deficits in reading, history was taken as the primary criteria for their diagnosis. If these studies confirmed the autosomal dominant pattern of reading disability that had been obtained historically, the family was included in the linkage study. Thus far, studies have been completed on nine such families. The linkage analysis employed 23 genotyping markers (i.e., variant gene products detectable by biochemical tests) and Q- and C-banding chromosomal heteromorphisms (i.e., different patterns of light and dark bands on chromosomes which are visualizable through a light microscope and which are transmitted genetically). These markers and heteromorphisms are each specific for particular portions of particular chromosomes and as a group potentially cover all 22 pairs of autosomes in the human genome. The results of the linkage analysis were that all loci tested gave lod scores less than 1.0 (i.e., p > .10) except for chromosome 15, short-arm heteromorphisms, which gave a lod score greater than 3.0 (i.e., p < .001). Thus, the linkage analysis provides suggestive evidence for an autosomal dominant locus on chromosome 15 responsible for one subtype of familial dyslexia. This result provides support for Hallgren's (1950) theory of autosomal dominant transmission in at least one subset of dyslexics.

Moreover, one kindred has a much lower lod score, suggesting that it does not show linkage to markers on chromosome 15. This could indicate that a second locus exists; however, a test for heterogeneity (Morton, 1956) is not significant. This points out one limitation of the linkage method in that decisions on localization for individual kindreds cannot be made unless the kindreds are large and by themselves give lod scores < -2 or > 3. Interestingly, most of the affecteds in this kindred appear to have a visuo-spatial dyslexia, whereas those in the other kindreds have good visuo-spatial skills and their dyslexia seems to be due to a subtle language processing deficits. A finding of two types of familial dyslexia with apparently different genetic loci would be consistent with the results of Omenn and Weber (1978).

All the probands in this sample were male, and the overall sex distribution of affecteds was 36 males and 19 females (1.89:1). This sex ratio is significantly greater than what would be expected for a pure autosomal dominant, but less than the
general population incidence. This sex ratio is also similar to that found in Hallgren's (1950) total sample and other familial samples discussed above. Affected females generally showed less severe reading and spelling problems than affected males. The increase above a 1:1 sex ratio in the present sample seems mainly due to a sex difference in gene expression, resulting in a bias of ascertainment favoring the more severely affected males. When probands are omitted, the sex ratio is not significantly different from 1:1. If the dyslexia locus interacts with the polygenic background of language abilities important for reading, and if there is a sex difference favoring females in those language abilities, then a difference in expression could be expected, as was discussed in the introduction.

Analysis of the phenotype in this sample of familial dyslexics to see if there is a consistent phenotype within and across families has involved the use of two test batteries. The first consisted of the Peabody Individual Achievement Test (PIAT), the WRAT Spelling Test, the Gray Oral Reading Test, the Colorado Perceptual Speed Test, and a set given to adults only. The second battery replicated the methods used by Mattis et al. (1975) to identify neuropsychological subtypes of dyslexics and used a modification (Camp & McCabe, Note 6) of the procedures described by Boder (1973) for identifying dyslexia subtypes on the basis of spelling errors. The results of the phenotype analysis thus far are summarized below.

1. Not surprisingly, affecteds were significantly poorer than their unaffected relatives on oral reading; reading comprehension; and, especially, spelling, confirming that they are dyslexic.

2. Nearly all of the affecteds showed average or above average scores on the PIAT Math or General Information subtests, near average scores on reading comprehension, but depressed scores on the tests involving oral reading and spelling. This suggests that their underlying deficit affects the ability to use letter-sound correspondences in reading and spelling, but does not affect the conceptual aspect of reading or other conceptual skills.

3. There was evidence for phenotypic variability at the level of academic skills, in that eight affected relatives showed a global learning disability on the achievement tests and were below average in all academic skills. They might correspond to the mixed subtype described in other research.

4. Few affected children or adults fell into a Mattis et al. (1975) subtype. Most were classified as normal. There were very few diagnosis main effects in an analysis of variance of all the tests in the Mattis battery, suggesting that these dyslexics have fewer neuropsychological deficits than do many populations identified clinically. In this respect, these dyslexics are somewhat similar to the relatively specific reading-disabled subtype identified in the Colorado Family Reading Study (Decker & DeFries, 1981), and the unexpected subtype identified by Satz and Morris (1980), though in the absence of similar measures, this comparison cannot be tested. When age differences were covaried out, significant diagnosis main effects were only found for tests of word retrieval, auditory discrimination of words in a noise background, and short-term verbal memory span. This suggests a subtle language-processing deficit involving either lexical retrieval, phonemic awareness and segmentation skills, or phonological memory, or some combination of these.

5. The affecteds were significantly more likely to fall into a Boder (1973) category (always the dyseidetic category) than the unaffecteds. However, about one-third of the affecteds were classified as normal, even though their spelling errors differed significantly from unaffecteds in the use of both simple phonetic rules and more complex orthographic rules (Pennington et al., Note 2). The designation “dyseidetic” is misleading because the affecteds so classified do not have a visuo-spatial or visual memory deficit; moreover, a significant proportion of their errors are dysphonetic in that they violate simple phonetic correspondences. A more complex view of spelling errors is needed to describe these dyslexics, one which incorporates developmental changes in spelling strategies.

6. Some aspects of the phenotype show developmental changes (e.g., their reading comprehension skills and their spelling strategies), whereas others do not (e.g., their problems with lexical retrieval and phonological memory). Further research is needed to elucidate the interrelationships involved.

A few comments are needed regarding the results of the linkage analysis in this study. Though the results support an autosomal dominant locus on chromosome 15 involved in the transmission of dyslexia, it is important to see if this linkage holds up in a larger
sample. Several kindreds have been recruited and tested, but the linkage analysis of them has not been performed as yet. Second, the positive linkage found here did not depend on an association between a given marker and dyslexia. Rather the marker and its particular value (i.e., fluorescence level) varied across kindreds; what was invariant was the association between a pattern of markers and dyslexia within kindreds. This makes it unlikely that the markers themselves are involved in the transmission of dyslexia.

In summary, we have traced the development of research on the genetics of dyslexia. It is clear at this point that some forms of dyslexia are transmitted genetically and that there are likely to be several forms of familial dyslexia involving different modes of transmission. Dyslexia does not appear to be a sex-linked disorder, but there is a sex difference in expression, likely due in part to normal, genetically based sex differences in language skills. There are different dyslexia phenotypes, developmental changes within a phenotype, and phenotypic variability across family members of similar age. All these sources of phenotypic variability make it more difficult for the investigator to test whether a given phenotype runs true within a family. Little is known about the developmental precursors of familial dyslexia in early childhood, except that there are rarely obvious delays in language or other milestones. A longitudinal study of infants within affected families is needed to provide information in this area. Finally, the case of dyslexia illustrates many of the genetic methodologies that may be applied to the investigation of a learning disability or other behavioral trait which appears to be familial. The main type of study not found here is an adoption study, mainly due to the difficulty of ascertaining enough dyslexic parents who relinquished their children.

**Speech and language disorders.**—This is a broad category which includes many different specific disorders, some of which co-occur significantly with reading and spelling problems. In fact, some authors consider dyslexia and speech and language problems to be part of the same syndrome (e.g., Ingram, 1959; Owen et al., 1971). In this vein, Hallgren (1950) used the presence of speech problems as the main diagnostic criterion in some of his cases of dyslexia. In contrast, some dyslexia investigators (e.g., Symmes & Rapaport, 1972) exclude speech and language problems in their diagnosis of dyslexia, and it is a common finding in many samples of specific dyslexics that there is no history of speech or motor milestone delays or later articulation problems.

The position taken here is that there are a variety of both speech and language disorders, that there may be pure speech disorders without language involvement, and that speech and language problems significantly increase the risk for reading and spelling problems, but that dyslexia is nonetheless a separate syndrome which can occur in the absence of readily detectable speech and language problems. In our clinical experience, we have seen children who represent a number of possible combinations of these different disorders, including children with definite speech and language problems but surprisingly good reading and spelling ability. Obviously these problems in phenotype definition have important implications for research on both dyslexia and speech and language problems.

There are much fewer data on the genetic bases of speech and language problems, although studies of normal populations definitely support the inheritance of speech and language abilities (e.g., DeFries, 1980; DeFries & Plomin, 1978). McCreary (1926) reported a positive family history in one-third of all children in a clinical sample with congenital auditory impairment, that is, a receptive language deficit affecting word discrimination. Ingram (1959) reported on a clinical sample of 80 children with specific developmental speech disorders, which he defined as delayed articulation development, especially of consonant sounds. Eighteen patients (23%) had a parent with a history of speech defect, and 24 patients (20%) had siblings with speech problems. Of those patients with affected siblings, 23 (98%) had one or more siblings with articulation problems similar to those of the patient, providing strong evidence of familial similarity in phenotype in this group. The sex ratio in the entire sample was 2.64:1, males to females. In Owen et al.'s (1971) family study of learning disorders, she found that, of 20 educationally handicapped children in the PIQ > VIQ subgroup—which showed the greatest familial aggregation for reading problems—there was also a significant incidence of articulation problems requiring speech therapy in both probands (45%) and their siblings (35%), a result similar to Ingram's (1959). More recently, it has been reported that some cases of Renpenning syndrome, a form of X-linked
Pedigree inspection ruled out simple autosomal dominant, autosomal recessive, or X-linked modes of inheritance. The data were compatible, however, with the predictions of both polygenic and single-gene inheritance when environmental modification and differential thresholds for sex were considered. The polygenic threshold model has been described above. When their data were analyzed using this model, the predicted frequency of stuttering (lifetime prevalence) among males was 4% and among females was 2%, in good agreement with the available data. Eighty-seven percent of the variance in fluency among individuals was found to be attributable to genetic influence using this model.

The single major locus model is somewhat more complex, but deserves detailed comment, since it may be applicable to other language and learning disabilities. A two-allele system was hypothesized, with the phenotypes of each of the three possible genotypes being modifiable by nongenetic factors. In addition, the genotypes would act differently in the two sexes. Thus, the homozygote for the "normal" allele would have less genetic susceptibility for stuttering, but given the right environmental factors might still stutter; the heterozygote would be at greater genetic liability, and the homozygote for the "stuttering" allele would almost always stutter, even if in a benign environment. Furthermore, heterozygous or homozygous females would show less genetic susceptibility than males with the same genotype.

Using this model, a gene with a frequency of 4% best explained their data. It predicted that the phenotypes of homozygotes would be almost totally genetically determined, but that among heterozygotes the gene would be penetrant in only 40% of males and 11% of females. The population frequency of affected males would be 4% and that of affected females would be 1%.

Severity of stuttering was not related to genotype in either model; in fact, the data indicated that severity or persistence of stuttering in the proband was not related to frequency of stuttering among relatives. A possibility that these investigators are considering is that of a two-locus system, with one gene influencing stuttering and the other influencing recovery.

Another disorder which may show learning disabilities and/or speech and language disorders is the Gilles de la Tourette syn-
This syndrome is characterized by involuntary tics and vocalizations, including coprolalia. Family clustering as well as therapeutic response to haloperidol suggest a genetic etiology, but as yet the exact mode of inheritance is unclear and may be heterogeneous (Eldridge, Sweet, Lake, Ziegler, & Shapiro, 1977; Nee, Caine, Polinsky, Eldridge, & Ebert, 1980; O'Quinn & Thompson, 1980; Wassman, Eldridge, Abuzzahab, & Nee, 1978). (It should be noted that the data from one study, Golden [1978], which purported to demonstrate autosomal dominant inheritance, was improperly analyzed.) O'Quinn & Thompson (1980) noted speech and language problems in four out of five probands with Tourette syndrome, and all five had some academic problems, particularly with writing and mathematics. Nee et al. (1980) found a history of learning disability in 20 of 50 patients, and Eldridge et al. (1977) commented on reading disability in 3 of 21 propositi.

We could find few other studies pertaining to the genetic bases of speech and language disorders, which is surprising given that the incidence in children of these disorders is roughly 5%-10% and given the above-mentioned evidence for familial aggregation. The example of familial dyslexia should alert potential investigators to the many methodological issues involved in studying the inheritance of a complex behavioral phenotype and thus lead to more effective research.

Other learning disabilities.—A number of other specific LDs have been identified clinically, including specific arithmetic problems, specific memory problems, specific conceptual and organizational deficits, and developmental apraxia and agnosia (Walton, Ellis, & Court, 1962). This last syndrome encompasses children with fine and gross motor skill deficits, motor planning problems, and visuo-spatial and constructional problems. These children are clumsy, and have trouble with dressing themselves, and with drawing and printing, despite average intelligence. In our clinical experience, these symptoms can occur singly. We were unable to find any studies which examined the possible influence of genetic factors in these various LDs, though we have occasionally found a positive family history in patients with some of these specific disorders. Thus, future investigations might yield evidence of genetic influence in these disorders.

Review of Studies of Populations with Documented Genetic Alterations

This section is concerned with studies which in most cases take the opposite approach to that discussed above. Instead of beginning with the phenotype and working "backward" to the underlying genotype, if any, the following studies begin by identifying a population with a common abnormal genotype and then see if this leads to common abnormalities in cognitive phenotype. If appropriate controls are used, the genetic causation of group deficits is readily inferred. Two examples of this approach will be reviewed below, sex-chromosome anomalies (SCAs) and treated PKU. In addition, we will briefly discuss minor autosomal anomalies.

Sex-chromosome anomalies.—Soon after Tjio and Levan (1956) developed a method to reliably count the number of human chromosomes, it was discovered that the Turner syndrome in females and the Klinefelter syndrome in males were both associated with abnormal sex-chromosome number (i.e., 45,X and 46,XXY, respectively). Somewhat later, two other examples of abnormal sex-chromosome number were discovered—47,XXX females (Jacobs, Baikie, Court Brown, MacGregor, MacLean, & Harnden, 1959) and 47,XXY males—neither of which was associated with an obvious physical syndrome. Screening studies of mental and penal institutional populations eventually established a nonartifactual, increased prevalence of 47,XXY, 47,XXX, and 47,XXY individuals in such settings (see Hook, 1978, and Polani, 1977, for reviews). Interestingly, in these various screening studies, 45,X females have not shown a similarly increased risk for mental or penal institutionalization as adults, though they appear to have a somewhat increased risk for retardation and learning disabilities. Group data also document clearly that 45,X adults and adolescents have normal verbal IQs but depressed performance IQs, as well as increased difficulty on a variety of other tests of spatial abilities.

However, the above screening studies of SCA individuals shed little light on the developmental processes which placed some of these individuals at increased risk. Moreover, such studies provided no information about the overwhelmingly large majority of such individuals who were not institutionalized. Screening studies of child populations, either
in special educational classes or child psychiatry clinics (e.g., Eriksson, 1972; Fujita, Yushida, Tanigawa, Yamauto, & Sakamoto, 1972), also found an increased risk for mental retardation and behavior problems, but, in addition, suggested an increased risk for learning disabilities. Retrospective reports on SCA adults also suggest an increased incidence of learning disabilities in childhood (Hier, Atkins, & Perlo, 1980; Olanders, 1967). Once again such studies do not provide information about either the development of these possible LDs or the range of phenotypic variation among the SCA individuals.

To provide unbiased information about the incidence and normal developmental history of these conditions and the range of variation among SCA individuals, several longitudinal studies were undertaken of unbiased populations identified at birth (see Robinson, Lubs, & Bergsma, 1979). What has been learned about the development of learning abilities and disabilities in SCA children is summarized below. The incidences of 47,XXY, 47,XYY, and 47,XXX individuals among newborns are all about 1.0 per thousand live births of the same sex; the incidence of 45,X individuals is about 0.1. Thus, LDs and SLDs attributable to these anomalies make up only a very small proportion of the total LD and SLD population. One main finding which needs to be strongly emphasized at the outset is the degree of phenotypic variability among affected individuals, such that some children in each karyotype group are completely normal. Thus, what is presented below concerns group findings.

Children in all four karyotype groups (45,X; 47,XXX; 47,XXY; and 47,XYY) have overall IQs which are somewhat depressed relative to siblings and normal controls, indicating that sex chromosome aneuploidy has a general effect on cognitive development. This would be expected, since the genetic change involved is a quantitative one. However, in addition to this general effect, there are also specific effects which vary across karyotypes. Within all the karyotypes having an extra sex chromosome (i.e., 47,XXX; 47,XXY; and 47,XYY), there is a definite impact on speech and language development, manifested by delayed speech milestones and depressed verbal IQs. These speech and language difficulties would help to explain the increase in learning problems observed in all three of these groups, since most academic skills are language based. It is also interesting that it is these three groups who are at greater risk for later emotional and behavioral problems, in contrast to the 45,X females. It seems likely that speech and language deficits could interfere with normal social and emotional development and place an individual at greater risk for problems in those areas.

Of these three karyotypes, 47,XXY males appear to be most specifically affected in language development. Relative to siblings and controls, a number of studies have found that they are depressed in verbal IQ only (Pennington, Bender, Puck, Salbenblatt, & Robinson, 1982; Graham, Bashir, Walzer, Stark, & Gerald, Note 7). This same pattern has been observed in all the other studies of randomly ascertained samples of XXY children, including one study of a non–English speaking population (Robinson et al., 1979), and thus appears to be a very consistent phenomenon. These studies also found that XXY boys as a group had delayed speech and language milestones. Consistent with these findings, their school problems are more likely to involve difficulties in reading and spelling (Pennington et al., 1982). There have been two studies (Bender, Fry, Pennington, Puck, Salbenblatt, & Robinson, in press; Graham et al., Note 7) which have examined the speech and language problems of these boys in detail. Graham et al. (Note 7) found significant reductions in auditory processing rate; auditory-verbal, short-term memory; word retrieval; and expressive syntax, whereas receptive language was relatively normal. Bender et al. (in press), in a blind study of SCA children and matched siblings, also found problems in both auditory-verbal, short-term memory and expressive language, including word retrieval, but they also found more pronounced difficulties with receptive language. Both studies agree that various aspects of language processing are the main deficiency in these boys rather than the conceptual or symbolic use of language. Thus, XXY boys are like other children who present with a fairly specific developmental dysphasia, presumably involving mainly left-hemisphere dysfunction.

The 47,XXX females exhibit a more global delay, which is evident as early as 1 year of age in the form of milestone delays and depressed performances on developmental assessments. Later IQ assessments at ages 4 and 8 showed that both verbal and performance IQ values are significantly depressed below those of siblings (Pennington, Puck, &
Robinson, 1980). Consistent with these find-
ings, 47,XXX girls, compared with both 45,X girls and 47,XXY boys, were more likely to have learning problems, and when they did, generally had global learning problems (Pennington et al., 1982). This finding is consistent with the nature of their speech and language problems, which were more severe than those found in the other groups and which "reflected a generalized deficit in the comprehension of symbolic language and syntax" (Bender et al., in press). All of these results are consistent with the idea that 47,XXX females as a group suffer from a general conceptual deficit as well as a developmental dysphasia. Another study of a newborn sample of 47,XXX females (Rovet & Netley, Note 8) has found they have more specific speech and language problems than were reported by Pennington et al. (1980). Thus, IQ data and speech and language measures are needed on other samples to clarify this issue.

Of these groups with extra sex chromo-
somes, the cognitive phenotype is least well defined in 47,XXY boys. This is partly due to the fact that cytogenetic procedures to screen for an extra Y chromosome were developed later than those for extra X chromosomes. Consequently, the newborn samples of 47,XXY being followed in various centers are both smaller in number and younger. The intellectual depression in 47,XXY children appears to involve both verbal and nonverbal abilities, though verbal abilities seem more affected. Similarly, early speech and language milestones are more likely to be delayed than motor milestones (Robinson et al., 1979). The four XYY boys in the study of Bender et al. (in press) showed speech and language deficits similar to those of the XXY boys. It is also of interest that a number of studies have reported an increased incidence of hyper-
activity in XYY children, which is not found in XXX girls or XXY boys (Hier et al., 1980). Further research is needed to delineate the kinds of learning disabilities exhibited by XYY boys.

In contrast to the findings for children with extra sex chromosomes, speech and lan-
guage development in 45,X girls as a group is much more normal and their most notable deficits are in nonverbal areas. Unlike the other karyotypes, they do not exhibit delays in either early speech or motor milestones (Robinson, Puck, Pennington, Borelli, & Hudson, 1979). The depressed performance IQ reported for many samples of adults and adol-
scents is observable as early as age 4 (Pennington et al., 1982), as are related problems on various drawing and design-copying tasks. In school, they do show an increased risk for learning problems relative to siblings and, unlike the other SCA children, frequently have problems in handwriting develop-
ment because of their visuo-spatial prob-
lems (Pennington et al., 1982). They are also more likely to exhibit an attention deficit in the preschool and early elementary years. In contrast, their reading and spelling develop-
ment is normal. Although the main deficit in 45,X girls is in nonverbal areas, some recent studies have found evidence for speech and language difficulties as well, including problems in speech production; audi-
tory-verbal, short-term memory; and receptive language (Bender et al., in press; Bender, Note 9). These results are hard to interpret because the attentional problems of these girls might interfere with their ability to hold longer verbal sequences in short-term memory. In addition, 45,X girls frequently have high arched palates and chronic serous otitis media, both of which would impact on speech production.

More work has been done on the neuro-
psychological basis of the cognitive deficits in Turner syndrome than those found in other SCA individuals. Although earlier work had suggested involvement mainly of the right parietal lobe (Money, 1973), more detailed neuropsychological investigations have found evidence for more widespread right-hemi-
sphere dysfunction (Kolb & Heaton, 1975; Silbert, Wolf, & Lillienthal, 1977) or even bilateral dysfunction, including frontal lobe dysfunction (Waber, 1979). Frontal lobe dysfunction would help explain the attentional deficit reported in these girls; it would also affect mathematical reasoning and organiza-
tional skills generally. A recent study using both an extended Halstead Reitan neuro-
psychological battery and auditory- and visual-
evoked potentials during complex information processing found right-hemisphere dysfunc-
tion with the most marked dysfunction in the right temporal lobe, as well as evidence for some frontal lobe and left-hemisphere dys-
function (Shucard, Pennington, Shucard, & Cummins, Note 10; Pennington, Shucard, Pendleton, & Heaton, Note 11). In summary, it appears that 45,X females have predomi-
nantly right-hemisphere dysfunction, which is not focal, and which is not exclusively visuo-
spatial in nature.
Treated PKU.—Children treated early for PKU (and thus spared mental retardation) have been followed longitudinally by a collaborative study involving a number of centers. Some of these children went off dietary treatment at around age 5 or 6, whereas others have remained on diet. The prevailing medical opinion has been that dietary treatment through the preschool years was sufficient to prevent the toxic effects of excess phenylalanine upon the developing central nervous system. However, comparisons between the academic performance of children who remained on diet and those off diet have suggested an increase in learning disabilities in the latter group, despite normal IQs in both groups. A recent pilot study of 7 school-age PKU children (6 are off diet) found a surprisingly consistent pattern of neuropsychological deficits (Pennington, van Doornick, McCabe, & McCabe, Note 12).

The performance of the PKU children on an extended Halstead Reitan neuropsychological test battery was compared with that of four other groups of children: specific dyslexics and three groups of children with documented brain damage, involving primarily either the left, right, or both hemispheres. The PKU children, unlike any of the other groups, were more likely to be delayed in mathematics than in reading or spelling. They were more likely to be depressed on the performance subtests of the WISC-R than on the verbal subtests, and they gave evidence of deficits on tests of flexible thinking and conceptual skill (Category Test and Wisconsin Card Sorting Test), as well as tests of right hemisphere spatial abilities (Tactual Performance Test: left hand only, and a test of constructional praxis).

The PKUs were not completely like any of the four comparison groups, but are most similar to the right-hemisphere and bilateral groups and least similar to the specific dyslexic and left-hemisphere groups. These results do not justify a definite localization for the neuropsychological dysfunction in the PKUs, but they suggest that the dysfunction is somewhat generalized and possibly involves the right hemisphere and prefrontal areas more than the classical language areas. Neuropsychological dysfunction in these areas would help explain their problems in mathematics, attention, and organizational and planning skills more generally. It is interesting that these deficits, while not identical, show some similarities to those seen in 45,X females.

One hypothesis which would explain the different pattern of results in the PKU children is that they were taken off diet after the sensitive period for language development had largely passed. Therefore, unlike the dyslexics or dysphasics, their deficits did not involve language skills, but rather later-developing skills. These skills are subserved by brain areas which likely reach functional maturity later than the language areas in the left hemisphere. Obviously, further studies are needed to see if this pattern of deficits is found across larger samples of early-treated PKU children taken off diet and to test hypotheses concerning the neurological bases of these deficits.

Autosomal anomalies.—There are a few clinical reports of children with autosomal deletions or additions who are not retarded (as is the case for nearly all known chromosomal alterations in autosomes), but who rather have more specific deficits. For instance, deletion of the short arm of chromosome 18 (18 p–) produces a recognizable physical and cognitive syndrome, but with a wide range of severity (Schinzel, Schmidt, Luscher, Nater, Brook, & Steinman, 1974). Children with this deletion who have mildly retarded or borderline IQs have mild physical involvement and quite distinct delays in expressive language and articulation. There are also a few nonretarded children with a small addition to chromosome 10 (10 p+) who have markedly depressed verbal IQs (Graham, Note 13). These few cases raise the distinct possibility that the increasing ability of cytogenetic techniques to find very small chromosomal abnormalities may reveal other regions in the genome involved in specific cognitive disabilities.

Discussion

These various examples of genetically influenced learning disabilities and speech and language disorders have both clinical and theoretical implications. On the clinical side, the heterogeneity of LDs and SLDs is impressive, both in etiology and phenotype, and thus careful differential diagnosis on the part of clinicians is important. More generally, the various types of genetically influenced LDs and SLDs discussed here may serve as models which will help advance our ways of classifying and treating LD and SLD children.

On the theoretical side, the conditions reviewed above have implications for de-
velopmental neuropsychology, specifically for how we think about cognitive and language development and its bases in brain development. Although there is little that is known in this area, some initial comments can be made.

First of all, it is important to note that many of the disorders mentioned above affect some aspect of speech and language functioning. This observation also holds for most developmental disabilities, regardless of whether the etiology is genetic or not, and suggests that the neural bases of speech and language development are vulnerable to many different kinds of influences during infancy and early childhood. This makes sense, given that the first 5 years of life may be viewed as the sensitive period for language development. Moreover, normal speech and language is subserved by a complex functional system which occupies a large portion of the cerebral cortex. This system could be disrupted at many different points. To understand both normal and abnormal speech and language development, a better nosology of developmental speech and language disorders, which identifies pure subtypes of disorder and relates each disorder to dysfunction in a particular component or components of the complex neuropsychological system subserving language development, is needed. Such a nosology would be analogous to the neuropsychological classification schemes which exist for the adult aphasias, except it would have to incorporate developmental changes in the localization of various speech and language functions. Some of the genetically influenced LDs and SLDs discussed above (i.e., dyslexia and stuttering) may represent rather focal and specific disruption of particular neural systems involved in speech and language development. Thus, just as adults with well-documented, circumscribed acquired lesions have taught us most of what we know about the functioning of the adult, human brain, children with discrete genetic alterations may tell us a great deal about the development of brain functions. The main difference is that studies of genetic alterations require that we take a developmental rather than a static view and also consider biological processes several steps removed from the brain itself.

A disorder such as specific dyslexia holds out the long-term prospect for being understood at all levels of analysis, including the genetic, neurobiological, neuropsychological, environmental, and functional. Some steps in the direction of this kind of understanding have already been taken for simpler behaviors. The neural bases of some well-established developmental milestones (e.g., the onset of the social smile and the beginnings of speech) are beginning to be understood, mainly in terms of regional cycles of myelination in particular parts of the developing brain (Konner, 1982; Yakovlev & Lecours, 1967). If this same approach can be extended to other, later functional milestones in the first decade of life, we would have a more solid theoretical framework on which to base our investigations of normal and abnormal cognitive and language development.

Second, it is clear from the various genetically influenced LDs and SLDs reviewed here that genetic factors can conceivably alter brain development through a large number of different pathways, including interaction between a specific genetic change and a particular environment. (For instance, some of the phenotypic variation across individuals with the same SCA seems clearly due to environmental differences.) The pathophysiology of a relatively simple genetic disorder, PKU, may include all of the following mechanisms: decreased myelination, decreased dendritic arborization, or interference in intraneuronal protein synthesis leading to decreased neurotransmitter production. In the more complex case of an additional sex chromosome quite a number of different mechanisms have been proposed, including changes in cell-division rate, steroid metabolism, neuronal migration rates, or sex-hormone levels (see Pennington et al., 1982). Netley and Rovet (Netley, 1977; Rovet & Netley, Note 8) have done a number of studies which have found an interesting relationship between measures of prenatal and postnatal growth rate (including dermal ridge count and bone age) and measures of hemispheric specialization in SCA children.

Overall, it is clear that progress toward further understanding of genetically influenced LDs and SLDs will require interdisciplinary research, including the efforts of geneticists, neuroscientists, child clinicians, and developmentalists.

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