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Reading disability: Evidence for a genetic etiology

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Abstract A review of evidence for genetic influences on reading disabilities (RD) is presented, with focus on twin study design and sib-pair linkage techniques. DeFries-Fulker multiple regression analyses result in significant estimates of heritability for group deficits on several reading and language measures. Structural equation modeling techniques reveal the presence of significant common and independent genetic effects on individual differences on reading skills. Finally, linkage techniques confirm a candidate locus for RD on chromosome 6.

Key words Reading disability (RD) – dyslexia – genetic – twin – linkage

Introduction

Behavior genetic studies are discovering compelling evidence that reading disability is a heritable disorder. Reading disability (RD) or dyslexia is characterized by specific deficits in reading and related language skills. Evidence for the genetic etiology of RD is presented here, using a multivariate description of specific RD deficits and distinct genetic analyses.

The accurate and efficient decoding or recognition of printed words is a primary deficit in children with RD. In addition, most subjects with a word-reading deficit also exhibit problems in other reading component skills, such as phonological decoding and orthographic coding, as well as in related language skills, such as phonological awareness (17). Behavioral genetic and linkage analyses of these reading and language measures are presented here within the context of the Colorado Learning Disabilities Research Center (CLDRC) (3), a highly collaborative research program, which has recruited a large sample of RD and control twins. Data from these CLDRC twins have been analyzed using behavioral genetic techniques to estimate the proportion of the group reading deficits that are due to genetic, shared environment, and non-shared environment influences. The existence of significant genetic effects on deficits for several different reading-related phenotypes raised the question of whether these genetic influences were due to the same or different genes. Structural modeling techniques have been applied to test for the commonality or independence of genetic and environmental effects on individual differences across different reading-related phenotypes. Finally, linkage studies have been carried out to map genetic factors influencing different reading and language related skills to specific chromosomal locations.

Twin study

The CLDRC is studying a large sample of twins and their families ascertained since 1982 from 27 school districts across the state of Colorado. First, school records are used to identify all twin pairs in a school. Then, twin pairs in which at least one of the twins has a school history of

reading problems are invited to the laboratory at the University of Colorado to undergo an extensive battery of standard psychometric and experimental tests. A comparison group of twin pairs in which neither member of the pair has a school history of reading problems is tested on the same battery.

The twin sample is currently composed of 1031 twin pairs, of which 618 pairs have at least one twin with RD, and 413 are normal twin pairs. The overall mean age of the twins at the time of testing is 12 years, ranging from 8 to 22 years. 481 are monozygotic (MZ), and 550 are dizygotic (DZ) twin pairs of which 224 are opposite-sex DZ twin pairs. Zygosity of same-sex twin pairs is determined by questionnaire (16) and, in cases of doubtful zygosity after this test, analysis of blood samples. Twins with evidence of serious neurological, emotional, or uncorrected sensory deficits are excluded from the study.

Twins and their siblings are tested on a large number of cognitive skills. The reading and language measures used in the present study have been extensively described elsewhere (17), but include word recognition (the recognition of printed words in isolation), phonological decoding (the oral reading of nonwords such as tegwop or framble), orthographic coding (recognition of words' specific orthographic patterns among phonological foils such as rain-rane or bear-bare), and phonological awareness (the ability to reflect on and manipulate the phonemic elements of speech).

Behavioral-genetic analysis

Twin designs allow to test for genetic influences on a trait (15). Identical or MZ twins have all of their genes in common, while fraternal or DZ twins only share half of their segregating genes on average. In addition, both types of twins are assumed to experience a similar influence from their shared environments. Consequently, if for a particular trait, MZ twins are more similar to each other than DZ twins, this similarity is assumed to be caused by their larger genetic resemblance.

Group deficits

The DeFries-Fulker (DF) multiple regression analysis of twin data (4) is a powerful test of genetic influence. This multiple regression technique is particularly appropriate for samples that have been selected for deviant scores on a continuous dimension such as reading. Affected individuals (i.e., probands) are selected as those who fall below a deficit criterion on the continuous dimension; the other member of each twin pair is termed the co-twin. A genetic influence on the trait would be indicated if DZ co-twins regress more than MZ co-twins towards the mean of the unselected population. This DF method also provides estimates of the relative influences on the trait of environmental factors shared and non-shared by the twins (4, 13, 5).

Table 1 Heritability (h_g^2), common environment (c_g^2) and non-shared environment (e_g^2) estimates for group deficits in each task. SE = standard error. * = $p < 0.01$; ★ = $p < 0.05$

Task	h_g^2 (SE)	c_g^2 (SE)	e_g^2
Word Recognition	0.45 (.08)*	0.49 (.10)*	0.06
Orthographic Coding	0.58 (.12)*	0.20 (.12)★	0.22
Phonological Decoding	0.61 (.10)*	0.24 (.11)★	0.15
Phonological Awareness	0.56 (.14)*	0.24 (.13)★	0.20

Analysis of our RD twin data using the DF model provides evidence of significant genetic and environmental influences on group deficits for several reading and language skills (Table 1). Genetic influences on deficits in word recognition, orthographic coding, phonological decoding, and phonological awareness are all significant, accounting for approximately half of the group deficits. Shared environment also significantly influences group deficits, with the strongest shared-environmental influence on word recognition. These results support the hypothesis of a genetic etiology for reading deficits, but at the same time suggest the pursuing question of whether the same or different genes are responsible for deficits in the different reading and language tasks. Olson et al. (17), using a bivariate extension of the DF model, presented evidence of significant genetic covariation among these measures.

Individual differences

Evidence for significant genetic correlations among reading skills can also be achieved by examining individual differences across normal variation of a continuous dimension, instead of analyzing the group deficits of the tail of the distribution. Structural equation modeling allows for the examination of genetic and environmental sources of individual differences. Maximum-likelihood model-fitting techniques can be used to compare MZ and DZ twin correlations and partition the observed variance into genetic and environmental components. In particular, the Cholesky decomposition, or triangular factorization

European Child & Adolescent Psychiatry, Vol. 8, Suppl. 3 (1999)

model, allows for the separation of common and independent factors accounting for the observed data (15, 14). In multivariate analysis of twin data, a typical Cholesky model includes triangular matrices of genetic, common environment, and non-shared environment factor loadings. In this model, the pattern of covariation among variables can be dissected into factors common to all variables, common to all except the first variable, common to all except the first two variables, and so on until a specific factor loads onto the last variable alone. The matrices of factor loadings reveals then the presence of factors common and/or independent to the phenotypes analyzed. An advantage of this Cholesky decomposition model is that it readily estimates the genetic correlations among the variables.

A Cholesky analysis of MZ and DZ covariance matrices from the RD sample produces significant genetic correlations among word recognition, orthographic coding, and phonological decoding. These correlations are positive and large, ranging from 0.68 to 0.90, supporting the idea that a large proportion of the genetic influences on RD must be common to the different reading components. This Cholesky analysis also provides evidence for independent genetic effects, which are specific to each reading task (8). In order to understand more precisely the relationship between genes and components of reading, linkage studies are necessary.

Linkage

Given that genetic factors affect a trait, linkage studies can subsequently attempt to map these genetic factors to specific chromosomal locations, assuming these genetic influences are due to genes with large impacts on the trait. Due to the great improvement in molecular genetic techniques in recent years, linkage methods have gained extraordinary popularity and have been applied to complex phenotypes, such as reading, which exhibit continuous variation of multifactorial nature. Quantitative Trait Loci (QTL) have been defined as such small segments of DNA containing one or several loci (genes) affecting a trait with continuous variation. A variety of linkage techniques exist, and the choice of a particular method of analysis depends on the kind of data available (21). At the CLDRC, a sib-pair approach is used with DZ twin pairs, which have the advantage of providing an extra control for age differences between sibs. Siblings of the twins have also been tested when possible. Twins, sibs, and their parents have been genotyped for genetic markers on a region of chromosome 6, which had been suggested previously as containing a QTL for RD (2, 9, 11). A recent multipoint regression analysis of continuous sib-pair data from an independent sample, using an extension of the DF model previously described (6, 1, 7), provides a confirmation of linkage of RD to the short arm of chromosome 6 (10). More specifically, both orthographic and phonological components of reading seem to be influenced by this QTL, as well as phonological awareness skills.

Conclusions

Both genetic and environmental factors contribute substantially to the development of reading deficits. Although environmental intervention, by means of reading instruction, alleviates RD symptoms in many dyslexic children (22), more efficient treatment strategies are still necessary for others. Behavioral genetic and linkage studies can enhance our knowledge of the etiology and potential treatment of RD in a number of ways. First, the heritable nature of specific RD deficits can help establish the true biological nature of dyslexia. Second, the identification of genetic risk factors may eventually translate into the possibility of early diagnosis of RD, with the additional advantage of timely remediation of language deficits that may be a proximal cause of many reading disabilities. And third, the identification of RD genes may eventually lead to major advances on the neuropsychological theories of reading skills and human cognition (18). For example, once genes have been identified, the study of their gene products and the areas of the brain in which they are expressed can shed light on the neurobiological foundations of reading skills. Furthermore, the recognition of genes affecting specific reading and language components might help understand the origin and possible comorbidity of RD deficits. For example, the possibility of a gene on chromosome 6 affecting simultaneously orthographic and phonological components of reading could explain the number of dyslexics experiencing deficits on both skills. Furthermore, other potential genes affecting RD have been suggested on chromosome 15 (20, 11) and on chromosome 1 (19, 12), which might in turn have their primary effects on a specific component of reading. If genetic influences are truly specific on reading components, and not part of a more general brain development failure, molecular neurogenetic analyses might ultimately help understand the biological nature of reading skills, and the relationship among deficits on the different reading components. Of course, these are scientific hypotheses to be studied in the future, but current studies are beginning to address these issues.

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