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Quantitative-Trait Locus for Specific Language and Reading Deficits on Chromosome 6p

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Summary

Reading disability (RD), or dyslexia, is a complex cognitive disorder manifested by difficulties in learning to read, in otherwise normal individuals. Individuals with RD manifest deficits in several reading and language skills. Previous research has suggested the existence of a quantitative-trait locus (QTL) for RD on the short arm of chromosome 6. In the present study, RD subjects' performance in several measures of word recognition and component skills of orthographic coding, phonological decoding, and phoneme awareness were individually subjected to QTL analysis, with a new sample of 126 sib pairs, by means of a multipoint mapping method and eight informative DNA markers on chromosome 6 (D6S461, D6S276, D6S105, D6S306, D6S258, D6S439, D6S291, and D6S1019). The results indicate significant linkage across a distance of at least 5 cM for deficits in orthographic (LOD = 3.10) and phonological (LOD = 2.42) skills, confirming previous findings.

Introduction

Developmental reading disability (RD), or dyslexia, is one of several distinct learning disabilities: "It is a specific language-based disorder of constitutional origin characterized by difficulties in single word decoding, usually reflecting insufficient phonological processing. These difficulties in single word decoding are often unexpected in relation to age and other cognitive and academic abilities; they are not the result of generalized developmental disability or sensory impairment. Dyslexia is manifested by variable difficulty with different forms of language, often including, in addition to problems with reading, a conspicuous problem with acquiring proficiency in writing and spelling" (Lyon 1995, p. 9).

The recognition of printed words is a key first step in reading comprehension, and it is regarded as the primary limitation on reading comprehension for children with RD (Stanovich 1988). Much research has focused on the component processes that contribute to individual variation and group deficits in reading performance, such as word recognition (WR), orthographic coding (OC), phonological decoding (PD), and phoneme awareness (PA; e.g., see Olson et al. 1989). Each of these reading and language skills is significantly heritable (Olson et al. 1994*a*), and most are genetically correlated (Olson et al. 1994*a* and in press; Hohnen and Stevenson 1995; Gayán and Olson 1997). In this report, we present new evidence for the linkage of a quantitative-trait locus (QTL) for several of these component skills to a small region on the short arm of chromosome 6.

Results obtained from a relatively small family study provided the first evidence for linkage of RD to chromosome 15 (Smith et al. 1983). Because of evidence for genetic heterogeneity, additional loci were examined, and a putative gene on chromosome 6 was also suggested (Smith et al. 1991). Subsequently, Cardon et al. (1994, 1995) reported significant linkage of a QTL for RD to the short arm of chromosome 6, including markers D6S105 and TNFB. In their study, a continuous measure of reading performance was based on the weighted composite of three subtests from the Peabody Individual Achievement Test (PIAT): WR, reading comprehension, and spelling (Dunn and Markwardt 1970). By means of an interval mapping procedure, results from two independent samples of siblings and fraternal twins suggested linkage for deficits in a composite measure of reading performance. However, they did not ascertain which specific component skills in reading and language may be responsible for the significant linkage for the

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composite measure. Gayán et al. (1995) subsequently used the same sample of fraternal twins and mapping methods to obtain evidence for linkage in the same chromosomal region for deficits in WR, PA, and OC.

More recently, Grigorenko et al. (1997) found evidence for linkage in approximately the same region of chromosome 6, for measures of PA that were similar to measures used in Gayán et al. (1995) and in the present study. They suggested that linkage in this region might also be present for single-word reading, although this phenotype was also significantly linked to markers on chromosome 15. More recently, Grigorenko et al. (1998) have also obtained some evidence for linkage to chromosome 1, a finding first reported by Rabin et al. (1993). The Grigorenko et al. (1997) sample consisted of extended families with a history of RD that strongly suggested a pattern of genetic transmission. In contrast, the samples of fraternal twins reported in Cardon et al. (1994), Gayán et al. (1995), and the present study were not specifically selected for evidence of familial transmission.

Results obtained from these previous linkage studies strongly suggest the existence of a reading-related QTL in a small region of chromosome 6, as well as in other regions of the genome, affecting at least some component skills related to reading ability. Using a new independent sample of 126 sib pairs from the Colorado Learning Disabilities Research Center (CLDRC; DeFries et al. 1997), we have confirmed the previous evidence for linkage to chromosome 6. Moreover, we have analyzed data for the specific reading-related component skills that appear to be most influenced by this putative gene, and we have located the QTL more precisely within the region already determined by previous studies.

Methods

Subjects

Subjects analyzed in the present study were 180 individuals (twins and siblings) in 79 families from the CLDRC (DeFries et al. 1997). This sample is composed of 60 families of two siblings, 16 families of three siblings, and 3 families of four siblings, yielding a total of 126 possible sib pairs and 101 independent sib pairs (computed as $n - 1$ per family of n sibs). This new sample of sib pairs is completely independent of the sample analyzed by Cardon et al. (1994). Twins were identified from school records in 27 Colorado school districts. We then sought permission from the parents to examine the twins' files for any evidence of a reading problem. Twin pairs in which at least one member of each pair had a positive school history of reading problems were selected and administered a battery of psychometric tests. A control group of twins with no school history of RD was also ascertained and tested. In addition, siblings of both groups of twins were administered the same battery of tests. This study was approved by the Human Research Committee of the University of Colorado at Boulder. The mean age for the twins and siblings was 11.5 years (range 8–19 years).

Phenotypic Measures

Subjects from the twin families were administered a large battery of tests during two 2.5-h sessions. Tests included in this battery are the Wechsler Intelligence Scale–Revised (Wechsler 1974, 1981), the PIAT (Dunn and Markwardt 1970), and other experimental tasks developed to assess reading and language skills such as WR, OC, PD, and PA (Olson et al. 1994*a*).

WR.—WR is typically measured in standardized tests such as the PIAT (Dunn and Markwardt 1970) by having subjects read across rows of increasingly difficult, unrelated words until they reach an error criterion. There is no time constraint in these standardized measures. Adults who had reading difficulties as children may eventually reach normal levels of accuracy in WR in a favorable environment for reading development, but their WR is likely to remain significantly slower than normal (Lefly and Pennington 1991; Bruck 1992). Thus a measure of fluent WR may be more likely to reflect genetic constraints on reading development (Olson et al., in press). Our experimental timed WR test (Olson et al. 1989, 1994*a*) assesses WR accuracy when single words are presented on a computer screen and the subjects' correct response is initiated within 2 s. Because of the time constraints, this test is expected to be more reflective of the demands of fluent reading (Olson et al. 1994*b*). In contrast, PIAT WR evaluates accuracy in the recognition of words presented in sequence across a page. A WR composite score was created by averaging the timed WR and PIAT WR Z scores.

OC.—Important component skills in the development of WR include OC and PD (Olson et al. 1994*b*). OC is defined here as the ability to recognize words' specific orthographic patterns. This is a particularly important skill in English, in which the same word sounds can be represented by different letter patterns. Two specific measures were administered to the sample, to construct a composite score for OC. One measure, the 80-trial forced-choice task (orthographic choice), requires the rapid recognition of a target word versus a phonologically identical background foil that is not a word (i.e., rain, rane; sammon, salmon; see Olson et al. 1985, 1989). A second measure, the 65-trial homonym choice task, requires subjects first to listen to a question such as "Which is a fruit?" and then to choose between a pair of homophones on the computer screen (e.g., pair, pear; see Olson et al. 1994*a*). Both of these measures were scored as the subjects' percentage of correct answers. The OC composite score was computed as the

average of a subject's orthographic choice and homonym choice *Z* scores.

PD.—PD is typically measured through the oral reading of pronounceable nonwords. This skill provides a "self-teaching" mechanism to help support the correct reading of unfamiliar printed words (Share 1995). Children with reading difficulties tend to be significantly weaker in this skill than would be expected from their level of WR (Rack et al. 1992). As in WR, accuracy in reading nonwords may be improved through a favorable environment (Wise and Olson 1995), but accurate and fluent PD may be more constrained by constitutional factors (Olson et al., in press). PD was measured by a 85-item oral nonword reading task (e.g., ter, strale, lobsel; see Olson et al. 1989, 1994*a*). *Z* scores for accuracy and median correct reaction time were combined to produce a composite score.

PA.—PA, the ability to reflect on and manipulate the phonemic elements of speech, is an important predictor, in prereaders, for later reading success (Wagner et al. 1994). It is highly correlated with WR and even more so with PD, once reading instruction has begun (Olson et al. 1994*a*). Two measures of PA were included in the test battery. The 45-trial phoneme transposition task is a "pig latin" game in which subjects are required to take the first sound from the beginning of a word, put it at the end, and add the sound "ay." For example, "rope" would become "ope-ray." Subjects' scores were based on percentage of correct responses. The 68-trial phoneme deletion task presents subjects with a spoken nonword, which they are asked to repeat. They are then asked to remove a specified phoneme from the nonword, and, if they do this correctly, the result is a word (e.g., "say 'prot,'" "now say 'prot' without the 'r' sound" —"pot"; see Olson et al. 1994*a*). The final score is the percentage of correct responses. A PA composite score was created by averaging the phoneme transposition and the phoneme deletion *Z* scores.

Subjects' scores in each of these tasks were age regressed and expressed in standard deviation (SD) units relative to the estimated average score for the normal population. The population average was estimated from the large twin database available at the CLDRC. Within the sib sample analyzed in this study, all measures described above were approximately normally distributed, with group means 0.81–1.58 SD below the population average. Nonetheless, both measures of PA exhibited negative skewness due to the presence of a few lower scores, which extended the low tail of the distribution to 5.43 (phoneme deletion) and 6.01 (phoneme transposition) SD below the population average.

Genetic Markers

Eight informative DNA markers on the short arm of chromosome 6 (6p23-p21) were used in this analysis: D6S461, D6S276, D6S105, D6S306, D6S258, D6S439, D6S291, and D6S1019. These markers were selected to cover the linkage region reported by Cardon et al. (1994, 1995) and Grigorenko et al. (1997). Sibs and both parents from each family were genotyped with these markers according to methods described in Hall et al. (1996) and Idury and Cardon (1997). The number of alleles, heterozygosity, and relative chromosomal locations of each marker are shown in table 1. The chromosomal location of each marker was retrieved from the Genome Database (Johns Hopkins University). However, the accuracy of the order of markers D6S105, D6S306, and D6S258 may be questionable, since not all markers have been radiation-hybrid mapped or genetically mapped with high precision. The most recent marker order from physical maps of this area (Burt et al. 1996; Malfroy et al. 1997) has been used in the present study. The relative distance among markers, the number of alleles, and heterozygosity were computed from our sample.

Multipoint Sib Pair Analysis

We used a multipoint model-free procedure developed by Fulker et al. (1995) to analyze our sample. This is a regression-based method for estimating $\hat{\pi}_q$, the proportion of alleles shared identical by descent (IBD) for a putative QTL located at any position along the chromosome, given a particular constellation of marker genotypes assessed. The use of $\hat{\pi}_q$ has been shown to yield results highly similar to the IBD distribution approach of Kruglyak and Lander (1995) under most conditions (Fulker and Cherny 1996; Gessler and Xu 1996), but it has several computational advantages (Fulker and Cherny 1996). One of these advantages is important in analysis of data obtained from samples in which a proband has been selected for having an extreme score on a particular phenotype, as is the case with the data in the present article. Selection of extreme samples such as these can increase the linkage signal (Risch and Zhang 1995; Wijsman and Amos 1997). For such selected samples, use of the DeFries and Fulker (1985, 1988) regression procedure for sib data along with $\hat{\pi}_q$ for a pu-

Table 1

Marker Information

Marker	Location	cM	No. of Alleles	Heterozygosity
D6S461	6p22.3-p21.3	.0	11	.70
D6S276	6p22.3-p21.31	1.6	14	.76
D6S105	6p22.3-p21.31	3.9	14	.81
D6S306	6p23-p21.31	5.0	10	.61
D6S258	6p22.3-p21.31	5.0	12	.69
D6S439	6p21.33-p21.1	10.1	13	.68
D6S291	6p21.33-p21.2	11.6	7	.69
D6S1019	6p22-p21.1	14.7	12	.68

tative QTL is a simple, convenient, and powerful approach to data analysis. The regression equation

$$C = \beta_0 + \beta_1 P + \beta_2 \hat{\pi}_q, \quad (1)$$

where P is the proband's phenotypic score and C is the proband's cosib's score, is employed at 0.5-cM intervals along the chromosome. The point at which β_2 is greatest is the most likely position of the putative QTL, with β_2 estimating the additive genetic variance explained by the QTL and its associated t test providing a statistical test for linkage. If we assume a large sample, t^2 is approximately a χ^2, and an asymptotic LOD score can then be approximated by LOD $= \chi^2/(2 \ln 10)$. Carey and Williamson (1991) have extended this approach to include the effects of dominance by adding another regression coefficient and rearranging the $\hat{\pi}_q$ values.

Our sample of twins and siblings has been ascertained by selecting twin pairs in which at least one member of each pair has a positive history of reading problems. Moreover, probands have scores below a certain criterion on at least one of our standardized tests, and we can modify this criterion to select more-extremely affected samples of subjects. Because the mean score of this proband group is lower than the mean of the unselected population, the scores of cosibs will regress toward the population mean (Fulker et al. 1991).

Results

The phenotypic correlations for the set of variables employed in the QTL analysis were calculated for the full sib pair sample. All the bivariate correlations among the reading and language variables are positive, highly significant, and of moderate to large size, ranging from 0.41 to 0.90 in value.

Although our sample already had been selected for a history of reading problems, not all subjects exhibited low scores on all measures. Consequently, for initial analyses, an arbitrary criterion was determined such that, for each phenotype, subjects scoring lower than 2 SD below the mean of the normal population (28–76 sib pairs) were considered probands.

Table 2 summarizes the results obtained when the DeFries and Fulker method was applied to the phenotypic measures. In general, these results suggest the presence of a QTL on chromosome 6 that influences reading and language skills. We obtained similar, although less significant, results with the Haseman and Elston (1972) method, an unsurprising finding given that our samples are highly selected. The large LOD scores obtained for orthographic choice (3.10), PD (2.42), and the PA composite (1.46) confirm the previously reported linkage. Because results are presented for multiple phenotypes, a correction of statistical significance would be appropriate if nominal P values were reported. However, all of these measures are correlated; thus, a Bonferroni correction of nominal P values would be too conservative. Consequently, to quantify evidence for linkage, we report only LOD scores and sample sizes with no adjustment for multiple testing.

Table 2

LOD Scores, Number of Sib Pairs in Selected Sample, and Estimated Location of QTL

Task	LOD Score	No. of Sib Pairs	QTL Location
OC composite	1.90	28	.0
Orthographic choice	3.10	47	.0
Homonym choice	.39	35	5.0
PD	2.42	54	2.0
PA composite	1.46	39	5.0
Phoneme transposition	.91	40	5.0
Phoneme deletion	1.16	46	1.5
WR composite	.09	74	1.5
Timed WR	.21	68	14.5
PIAT WR	.05	76	1.5
IQ	.09	54	1.5

NOTE.—Proband selection criterion was 2 SD below the mean of unselected population. Location given is relative to marker D6S461, moving proximally along the chromosome.

Nonetheless, the evidence for linkage varies among the phenotypes, which suggests that this QTL may differentially influence different measures of reading and language performance. With respect to orthographic skills, there is significant evidence of a QTL effect on the OC composite score, which is mainly due to the very significant effect on the orthographic choice variable. In addition, PD and PA skills are influenced by this gene. Although there is some limited differential regression of WR scores by IBD, this effect does not reach statistical significance in this sample. Finally, in agreement with results reported by Cardon et al. (1994), there is no evidence for a significant effect of this QTL on IQ.

The results in table 2 indicate the presence of a QTL in a region of at least 5 cM that extends from marker D6S461 to D6S306–D6S258. Figure 1 shows the LOD scores obtained by fitting the DeFries and Fulker model to our phenotypic measures across the chromosomal region defined by our markers. The one-LOD support region for orthographic choice and PD covers approximately this 5 cM region. To locate more accurately the QTL, analyses were repeated with several different proband criterion points (1, 1.5, 2, 2.25, and 2.5 SD below the unselected group mean). When the maximum LOD scores obtained for the two most significant measures, orthographic choice (2.25 SD) and phoneme deletion (2.5 SD), are plotted (fig. 2), the peak of the linkage curve is ~2–3 cM proximal to D6S461 in a region flanked by markers D6S276 and D6S105.

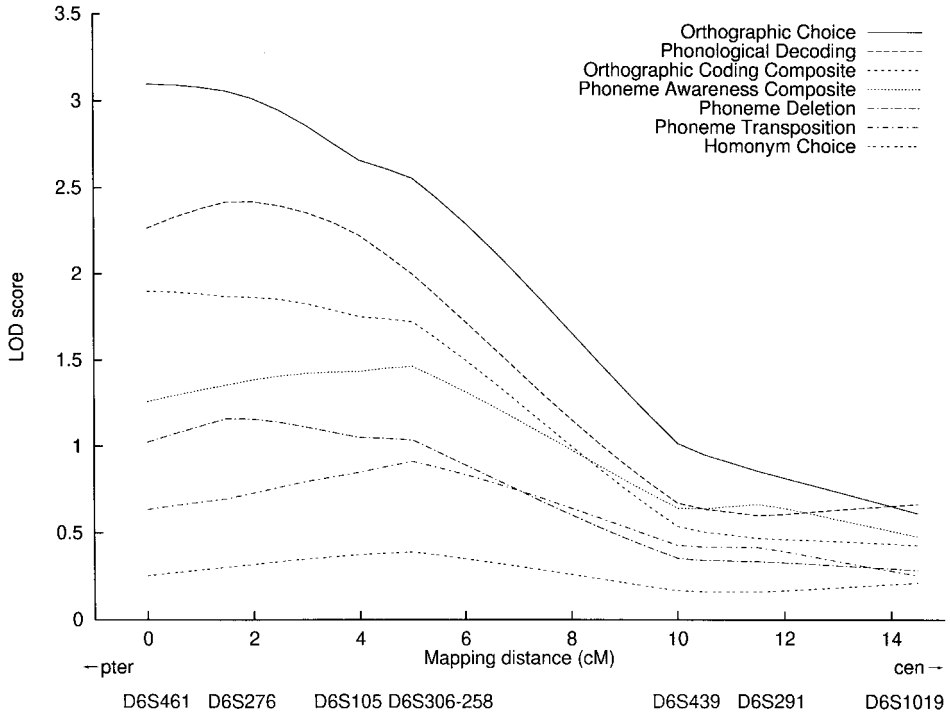

Figure 1 LOD scores for DeFries and Fulker model test of linkage (<−2.0 proband criterion). Chromosomal location is expressed in centimorgans proximally from marker D6S461.

Discussion

Although reading difficulties are due in part to genetic influences, localizing the individual genes that affect reading performance has been a difficult task. This has been true in part because of the complexity of the phenotype. Nevertheless, the extensive research on reading, by cognitive neuroscientists, has helped identify the key components of the reading process: WR, OC, PD, and the language-related skill of PA. In addition, the rapid development of resources and methodology in the field of human and molecular genetics within the past several years now provides the means to search for those QTLs that affect reading performance and other human behaviors.

Previous linkage studies strongly suggest the existence of a reading-related QTL on the short arm of chromosome 6. The present study provides confirmation of this linkage by presenting significant results of multipoint interval-mapping sib pair QTL analyses for several reading and language measures.

Reading performance can be decomposed into several component processes such as WR, OC, and PD, as well as other language-related processes like PA. All of these reading and language skills exhibit a significant genetic contribution (Olson et al. 1994*a*). Previous linkage studies have suggested the existence of QTLs for RD in different parts of the genome, with the possibility that different QTLs affect different components of the reading process (Grigorenko et al. 1997); however, our previous analyses suggest a large commonality among all of these reading and language measures. Phenotypic analyses of individual differences in several measures of PA, PD, and OC suggest a common factor for phonological skills (PA and PD) and a second correlated factor for OC (Olson et al. 1994*a*). Furthermore, the results of behavioral genetic analyses have suggested both common and independent genetic influences on phonological and orthographic skills (Olson et al. 1994*a* and in press). Most importantly, a large proportion of this genetic influence seems to be common to these reading components (Gayán and Olson 1997). Hence it is unlikely that the QTLs influencing these component reading skills will be completely distinct, although some of these QTLs may influence one skill more than the other. The extent to which individual QTLs influence different components of cognition is a fundamental issue for both behavioral genetics and cognitive neuroscience (Pennington 1997).

Previous findings have suggested that the chromosome 6 QTL influences general reading ability—in particular, PA and WR skills. Our findings reveal that both the orthographic and phonological components, and possibly WR (although to a lesser degree), are affected by the QTL. A recent independent analysis of family data

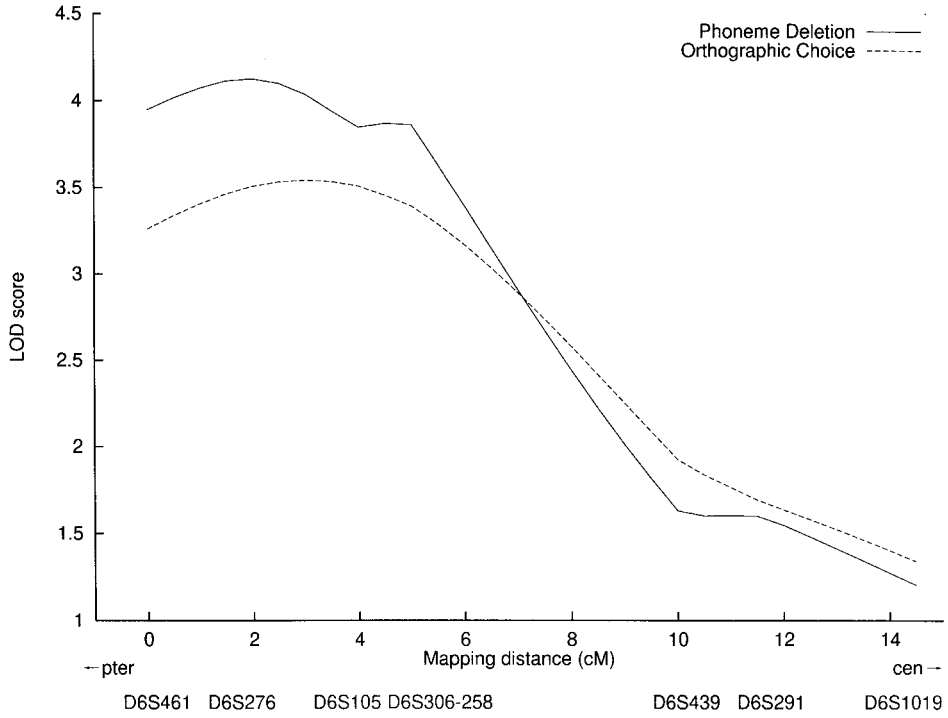

Figure 2 Maximum LOD scores obtained for orthographic choice (<−2.25 proband criterion) and phoneme deletion (<−2.5 criterion). Chromosomal location is expressed in centimorgans proximally from marker D6S461.

in the United Kingdom has found evidence for linkage of very similar phenotypes in exactly the same chromosomal region (Fisher et al. 1999 [in this issue]), which confirms the present findings. Other measures, including IQ, were not found to be influenced by this QTL. This result suggests that the putative 6p QTL affects several reading components and thus seems to contribute to the common genetic influence on reading. This conclusion is somewhat different from that of Grigorenko et al. (1997), who suggested that the QTL in this region may have a specific influence on the component skill of PA. In addition to obtaining significant evidence for linkage of PA to 6p, Grigorenko et al. (1997) also found significant linkage for PD skills to the same region, results that are in good agreement with those obtained in the present study.

We located the putative QTL to a region of several centimorgans on the short arm of chromosome 6. Results obtained from our multipoint interval mapping analyses indicate a region between markers D6S461 and D6S306–D6S258, and more specifically between markers D6S276 and D6S105. The 2-cM region identified by Cardon et al. (1994) is within this region (marker D6S105). Grigorenko et al. (1997) reported a region covering several centimorgans that overlapped this interval (D6S461 and D6S306) and extended distally relative to the present finding. It is important to note that discrepancies exist in the published genetic marker maps of this region. As a consequence, the genetic map used by Grigorenko et al. (1997) does not perfectly correspond to the one used in the present study. Markers D6S276 and D6S105, positioned proximally to D6S306 by Grigorenko et al. (1997), are localized by physical mapping distal to D6S306 (Burt et al. 1996; Malfroy et al. 1997), which defines an even more compact region of significance for linkage. Results obtained from an independent study (Fisher et al. 1999) have located the QTL in the D6S422-D6S291 interval, with a peak between markers D6S276 and D6S105, which closely agrees with our most likely location.

The results of the present analysis are unclear about the effect size and gene action of this putative QTL. Effect size calculations suggest that this QTL has a large impact on the trait, accounting for ~20% of the phenotypic variance of PD and phoneme deletion and as much as 60% in the case of orthographic choice. Reading is a complex cognitive process, and consequently multiple genes of relatively small effects are expected to contribute to its variability. Because the heritability of reading deficits is usually in the 0.4–0.6 range, these estimates of the QTL effect size seem large. One possible explanation for the apparently large effect size is the

selected nature of our sample. For example, if the QTL is rare, individuals with this genotype would be much more frequent in our selected sample than in the normal population, and consequently the heritability of the QTL might be increased.

In terms of gene action, no significant dominance variance was detected for most of the variables analyzed; however, this finding might be the result of low power to detect nonadditive effects. The only significant evidence for a dominant QTL was obtained for the orthographic choice variable ($t = 2.59$). Nonetheless, an examination of sib pair mean scores by IBD reveals the possibility of recessiveness, since, for most of the variables, sib pairs sharing both alleles are more alike than sib pairs sharing one allele or none.

Further analyses should be directed toward a better characterization of which component processes are affected by this QTL and a better quantification of the size of the effect for each phenotype. Moreover, the physical mapping and cloning of this gene could foster collaborative efforts between neuropsychology and genetics (Pennington 1997). The closeness of this putative QTL to the human leukocyte antigen region suggests the possible implication of a coding or regulatory gene related to the immune system on reading deficits. To clarify these issues, a larger sample of sib pairs, which we are currently obtaining at the CLDRC, will be required.

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Electronic-Database Information

URL for data in this article is as follows:

Genome Database, http://gdbwww.gdb.org (for chromosomal locations of markers used)

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