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Absence of Linkage of Phonological Coding Dyslexia to Chromosome 6p23-p21.3 in a Large Family Data Set

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Summary

Previous studies have suggested that a locus predisposing to specific reading disability (dyslexia) resides on chromosome 6p23-p21.3. We investigated 79 families having at least two siblings affected with phonological coding dyslexia, the most common form of reading disability (617 people genotyped, 294 affected), and we tested for linkage with the genetic markers reported to be linked to dyslexia in those studies. No evidence for linkage was found by LOD score analysis or affected-sib-pair methods. However, using the affected-pedigree-member (APM) method, we detected significant evidence for linkage and/or association with some markers when we used published allele frequencies with weighting of rarer alleles. APM results were *not* significant when we used marker allele frequencies estimated from parents. Furthermore, results were not significant with the more robust SIMIBD method using either published or parental marker frequencies. Finally, family-based association analysis using the AFBAC program showed no evidence for association with any marker. We conclude that the APM method should be used only with extreme caution, because it appears to have generated false-positive results. In summary, using a large data set with high power to detect linkage, we were unable to find evidence for linkage or association between phonological coding dyslexia and chromosome 6p markers.

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Introduction

Dyslexia and Its Genetic Basis

Dyslexia affects 3%–10% of school-age children (Lerner 1989) and is associated with major educational, social, emotional, and economic repercussions (Spreen 1988). Dyslexia may be defined as a specific difficulty with language-related functions (such as reading and spelling) that is independent of general intelligence and educational opportunity. Although many children with dyslexia have been shown to have visual perceptual deficits, impairments in timing of sensory processing, or poor attention/memory skills (Chase et al. 1996), most specialists concur that dyslexia is primarily a problem with processing the basic phoneme units of language (Van Orden and Goldinger 1996). Anatomical studies have shown that the brains of dyslexic individuals sometimes fail to demonstrate the usual asymmetric development in the language areas of the left hemisphere (Hynd et al. 1990; Duara et al. 1991; Leonard et al. 1993).

Familial clustering of dyslexia has been well documented for almost 50 years (Hallgren 1950; Zahalkova et al. 1972; Gilger et al. 1991), and twin studies show that the basis for at least some of this familial aggregation is genetic. For example, Bakwin (1973) reported a dyslexia concordance rate of 83% in MZ twins, compared with 29% in DZ twins. A genetic contribution to dyslexia was also supported by twin studies of reading and spelling (DeFries et al. 1987), with heritability estimates (controlling for general intelligence) of 0.51 for reading comprehension and 0.73 for spelling (Stevenson et al. 1987). Problems in word recognition are thought to be central to dyslexia. Olson et al. (1989), studying twins of whom at least one had dyslexia, showed that the phonological coding component of word recognition was highly heritable (0.93), whereas the orthographic coding component was not heritable. Although twin data indicate clear genetic influences on specific language disabilities, the mode of inheritance of dyslexia remains unclear, with suggestions including autosomal dominant, recessive, polygenic, and genetic heterogeneity

(Hallgren 1950; Finucci et al. 1976; Lewitter et al. 1980).

Chromosome 6 Linkage

Smith et al. (1983) reported significant linkage to the centromeric region of chromosome 15 in nine families, although not all families showed linkage. Addition of more families reduced the overall evidence for linkage to chromosome 15cen (Smith et al. 1990) but also suggested linkage to the long arm of chromosome 15 (Smith et al. 1991). However, Danish researchers found no support for chromosome 15 linkage (Bisgaard et al. 1987). When Smith and colleagues omitted one family with strong linkage to chromosome 15cen, the remaining families revealed linkage to the markers BF and GLO1 in or just proximal to the HLA region on chromosome 6p21.3 (Smith et al. 1991). Their HLA region finding was noteworthy because of a possible relationship between immunologic disorders and developmental learning problems (Gilger et al. 1992; Kaplan and Crawford 1994). Our own data had argued for a genetic basis underlying this relationship (Crawford et al. 1992). More-recent studies by Smith and colleagues (Cardon et al. 1994) of both the previously studied kindreds (n = 19) and a set of DZ twins (50 pairs), using highly informative DNA-based markers, demonstrated significant linkage in each data set to D6S105 and/or TNFB, which are separated by 2 cM. TNFB is 0.8 cM from BF, and both are within the HLA region at 6p21.3 (Cardon et al. 1994). They used a quantitative nonparametric method to analyze linkage to a composite score for reading performance.

In an attempt to replicate linkage of dyslexia to chromosomes 6 and 15, Grigorenko et al. (1997) studied six extended families with at least four affected individuals per family. Five separate phenotypes were analyzed, each measuring some aspect of reading-related skills. They detected significant linkage between phonological awareness and markers located *distal to* D6S105/TNFB at 6p23–p21.3, using nonparametric affected-pedigree-member (APM) analysis, but, interestingly, no significant linkage using LOD score analysis. The marker that gave the most significant linkage evidence was D6S299. A different phenotype, single-word reading, showed significant linkage to chromosome 15 by LOD score analysis but not by APM analysis. Unfortunately, they did not report details of results for any of the other phenotypes they examined, such as phonological coding. They interpreted their results as supporting the chromosome 6p linkage reported by Cardon et al. (1994), even though the regions showing linkage in the two studies did not coincide well; for example, they found no linkage to D6S105/TNFB (the most strongly linked markers in the Cardon et al. [1994] study), and they found significant linkage to the more distal marker D6S109 (for which Cardon et al. [1994] found no linkage). We report here results of analysis of 79 families with a minimum of two affected siblings for linkage of phonological coding dyslexia (PCD) to D6S105/TNFB, D6S299, and flanking markers on chromosome 6 (studies of linkage to chromosome 15 are ongoing).

Families, Material, and Methods

Families

Families were identified through children attending special schools for learning disabilities. All subjects were $\geqslant 8$ years of age, and each signed an appropriate consent form (parents gave written consent for minors) approved by the University of Calgary ethics review board. For a family to meet the criteria for entry into this study, a minimum of two siblings had to be diagnosed as having probable or definite PCD (for description of phenotype and testing, see below). In all cases, the identified sibling pair consisted of school-aged children. Participation was then requested of the parents of these affected siblings, all siblings aged $\geqslant 8$ years, and families of consenting second- or third-degree relatives with a reported history of reading problems. Of the 79 families who met the minimum entry criteria and provided blood samples for genetic testing, 49 were simple nuclear families (27 had two affected children, 18 had three affected members, and 4 had four affected members). The remaining 30 families were extended kindreds consisting of the core nuclear family, with at least two affected siblings, and additional branches with affected members. Sixteen of these extended families contained five or more affected members (seven with 5 affected, one with 6, two with 7, one with 9, two with 11, and the largest with 21 affected members). All subjects were of European ancestry, except for one African American parent and his two children. Many of the families appeared to exhibit autosomal dominant transmission of PCD in that at least one parent of an affected child was also affected. Bilineal pedigrees (two parents either affected or having affected relatives apart from their own children) were relatively common, suggesting the possibility of assortative mating. A total of 617 individuals gave blood for genetic typing, and 294 of these were diagnosed as probably or definitely affected with PCD. Among affected individuals, 62% were male (1.6:1 male:female ratio).

Phenotype Definition

Olson et al. (1989) found that the majority (80%) of children with dyslexia had impaired phonological coding skills and that these skills have a high heritability (0.93). Similarly, in a sample of 131 children with various levels of reading disability whom we have tested (independent

of the current study sample), 121 (92%) met our criteria for PCD (see below), whereas only 10 (8%) exhibited higher-level deficits (e.g., comprehension problems) but intact phonological coding skills (authors' unpublished data). Others have confirmed that impairment in phonological coding constitutes a fundamental deficit in most individuals with a reading disability (Pennington et al. 1987). Furthermore, scoring of phonological coding skills in adults, using pronunciation of nonwords, appears to be reliable (not strongly influenced by remediation). We therefore chose the specific phenotype of impaired phonological coding skills, PCD, as the basis for our linkage study.

Phonological coding skills were tested with the word attack subtests from the Woodcock Reading Mastery Test (Woodcock 1987) and the Woodcock-Johnson Psychoeducational Test—Revised (Woodcock and Johnson 1989). Phonological awareness was assessed by the Auditory Analysis Test (Rosner and Simon 1971), and spelling was assessed with the Wide-Range Achievement Test (Jastak and Wilkinson 1984). A short form of the Wechsler Intelligence Scale for Children was used to test subjects 8–16 years old (Wechsler 1974), and the short form of the Wechsler Adult Intelligence Scale was used to test adults (Wechsler 1981). An important part of each adult's assessment was an eight-item structured interview addressing the individual's history of reading problems.

Two learning disability experts (B. J. K. and a reading specialist) reviewed the test results for each subject. Scores on the word attack tests were the primary data used for phenotype classification; the other tests (spelling, auditory analysis test, and the reported history) assisted in refining the certainty of the category. Particularly for adults, cutoff scores could not be used rigidly for the phenotype definition, in part because some of the tests have published norms only through age 18 years and in part because of the importance of considering the clinical history. Thus, a consensual coding system was developed (see reliability data, below) with guidelines agreed on by both raters. For children, scores were considered indicative of impairment if there was at least a 2-year gap between chronological age and performance. For adults, the entire profile of test scores was considered, and particular weight was given to the structured interview. The investigators examined all of the test results and interview summaries and, by consensual coding, assigned each subject to one of five categories describing the certainty (not severity) of PCD phenotype: 1 = definitely unaffected, 2 = probably unaffected, 3 = uncertain, 4 = probably affected, and 5 = definitely affected. Any untested (e.g., dead) pedigree member required in the linkage analyses was coded as uncertain, even if family history strongly suggested the presence or absence of PCD in that individual.

Although the coding scheme was consensual, interrater reliability was calculated in a subset of 273 subjects for whom phenotype classification was assigned independently by the two specialists; interrater reliability was excellent ($\kappa = 0.844$), with the only disagreements being ones in which one rater invoked the "uncertain" category. In no case did one rater call a person affected and the other rater call the person unaffected.

Genetic Markers

For each subject, DNA was extracted from 18 ml whole blood by standard procedures using a salting out method (Miller et al. 1988) and was typed for microsatellite markers reported to show linkage to dyslexia (D6S299, D6S105, TNFB) as well as for flanking markers (F13A1, D6S89, D6S291, GLP1R). Figure 1 shows the relative map locations of markers, with approximate distances, in centimorgans, derived from Généthon maps (Dib et al. 1996), Cedar maps, and the Marshfield Center comprehensive human genetic maps. Primer sequences were obtained from the following published sources: Polymeropoulos et al. (1991, F13A1); Litt and Luty (1990, D6S89); Dib et al. (1996, D6S299); Weber et al. (1991, D6S105); Nedospasov et al. (1991, TNFB); Dib et al. 1996, D6S291); and Stoffel et al. (1993, GLP1R). Microsatellites were typed by standard autoradiographic methods (Weber and May 1989) as described elsewhere (Field et al.1996). Autoradiographs were scored independently by two persons, the differences were resolved, and the final reads were double-entered into the computer and verified, by means of the file-compare command, to minimize typographical errors.

Statistical Analyses

Linkage analysis and power estimates.—Parametric (maximum likelihood LOD score) analysis of linkage between a hypothetical PCD locus and each marker was performed by means of the FASTLINK version 2.1 modifications (Cottingham et al. 1993) of the LINKAGE program package (Lathrop et al. 1985). Individuals were categorized as unaffected (phenotypes 1 plus 2), affected (phenotypes 4 plus 5), or unknown (phenotype 3) with

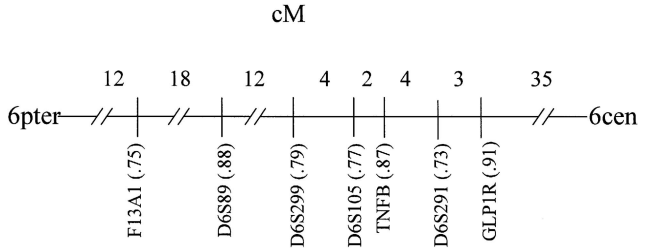

Figure 1 Map of markers studied (PIC in brackets)

Table 1

Models Used in LOD Score Linkage Analysis

	Model Number							
	1	2	3	4	5	6	7	8
Penetrances (aa, ab, bb)	0, .8, 1	0, .8, 1	0, .6, .8	0, .4, .6	0, .4, .6	0, .4, .6	0, 0, .8	0, 0, .8
Abnormal allele b frequency	.05	.01	.01	.01	.001	.25	.01	.25

respect to PCD. Since the aim was to replicate a reported linkage, a large number of models for the PCD susceptibility locus were tested, to decrease the chance of false-negative results (Vieland et al. 1993), including dominant, recessive, and intermediate inheritance models, all with reduced penetrance (see table 1). We calculated LOD scores at recombination (θ) values of 0, 0.01, 0.05, 0.1, 0.2, 0.3, and 0.4, using published marker allele frequencies from the Genome Database (GDB). Use of reduced penetrance allows individuals who possess a PCD-susceptible genotype to have, nevertheless, an "unaffected" phenotype, whereas use of the "unknown" category allows individuals whose test results are ambiguous to remain neutral with respect to PCD phenotype status but provides marker genotype information in the linkage analyses.

The power of the pedigrees to detect linkage by LOD score analysis was estimated by means of the SIMLINK program (Ploughman and Boehnke 1989), in which the 79 observed pedigrees were used as the basis for simulation of linkage between a 5-allele marker and a PCD-predisposing locus in 250 replicates of the pedigrees. Linkage was simulated at recombination (θ) values of 0% and 5%, for dominant and recessive models of PCD with penetrance 0.8, and with or without genetic heterogeneity (50% or 100% of families showing linkage to the marker).

Nonparametric affected-sib-pair linkage analysis was performed by means of the SIBPAL version 2.1 program from the SAGE package (Elston 1992). The core nuclear families of each kindred were analyzed; that is, the affected pair of siblings that brought the family into the study, both parents, and any other affected or unaffected siblings. All pairs of siblings were included; the resulting data set contained 190 affected sib pairs and 197 affected-unaffected sib pairs from the 79 core families. Marker allele frequencies for the sib pair analyses were estimated from the parents of the core families. (Note, however, that 85% of the core parents were genotyped, and therefore the sib pair analyses were not heavily dependent on marker allele frequencies.)

Linkage/association analysis.—Nonparametric APM analyses were performed with the APM program (Weeks and Lange 1988) to compare results directly with those of Grigorenko et al. (1997) and also with the newer SIMIBD program (Davis et al. 1996), which theoretically is less sensitive to misspecification of marker allele frequencies. These methods detect increased sharing of marker alleles between pairs of affected relatives that could be due to linkage or to association (linkage disequilibrium; Weeks and Lange 1988). Only markers D6S105, TNFB, and D6S299 (previously reported to be linked to dyslexia) were tested. Two sets of marker allele frequencies were employed: published allele frequencies from GDB and allele frequencies calculated directly from the parents of the 79 core families. All individuals in all kindreds were included in the analyses, with the exception that two large pedigrees were excluded from APM runs, since the program was unable to handle them. In the APM analyses, three different methods for weighting marker allele frequencies were tested: (1) no weight, (2) inverse of square root of allele frequency (higher weighting given to rarer alleles), and (3) inverse of allele frequency (strongest weighting to rarer alleles; Weeks and Lange 1988). In the SIMIBD analyses, *P* values were based on 1,000 simulated replicates.

Association analysis.—The core nuclear families were tested for association between PCD and each marker

Table 2

Pairwise Maximum LOD Score (θ)

	Model Number							
Marker	1	2	3	4	5	6	7	8
F13A1	0	0	0	0	0	0	0	0
D6S89	0	0	0	0	0	0	0	0
D6S299	0	0	0	0	0	0	0	0
D6S105	0	0	0	0	0	0	0	0
TNFB	0	0	0	0	0	0	.01 (.4)	0
D6S291	.61 (.3)	.62 (.4)	.36 (.3)	.19 (.3)	.16 (.3)	.35 (.2)	.38 (.3)	.10 (.4)
GLP1R	0	0	0	0	0	0	.08 (.4)	.02 (.4)

Table 3

SIBPAL Average Sharing in Affected Sib Pairs

Marker	Average Sharing	*P* value[a]
F13A1	.471	1.0
D6S89	.486	1.0
D6S299	.479	1.0
D6S105	.501	.48
TNFB	.497	1.0
D6S291	.525	.12
GLP1R	.518	.21

[a] One-sided *P* value for test of >50% sharing.

using the AFBAC program (Thomson 1995). This family-based association method compares the frequency distributions of marker alleles transmitted and not transmitted to affected children. Families were analyzed in two ways: (1) scoring alleles transmitted and not transmitted to the first affected child (simplex analysis), and (2) scoring alleles transmitted and never transmitted to the two affected siblings, weighting transmitted alleles by the number of transmissions (multiple sibs analysis; see Thomson 1995).

Results

Linkage Analysis

Table 2 shows the results of LOD score linkage analysis using the eight models in table 1. None of the maximum LOD scores reached the significant value of 3.0. For markers F13A1, D6S89, D6S299, D6S105, and TNFB, scores were negative across all θ values for all models (i.e., the maximum LOD score was 0 at $\theta = 0.5$). For D6S291, a maximum LOD of 0.62 at $\theta = 0.4$ was obtained (created primarily by two families) with the two dominant models, and, for GLP1R, a negligible positive LOD score (0.08) was obtained for one model.

Simulation analyses demonstrated that the power of the 79 pedigrees to detect significant linkage (LOD score >3) was 100% for both dominant and recessive models at both 0% and 5% recombination between the marker and PCD, under the assumption that all families have a form of PCD linked to the marker (no genetic heterogeneity). Even if linkage exists in only *half* of the families, the power to detect linkage remained excellent: at 0% recombination, power was >82% for a LOD score >3 and >92% for a LOD score >2, whereas, at 5% recombination, power was >74% for a LOD score >3 and >89% for a LOD score >2. Note that the actual microsatellite markers used had even more alleles (greater power to detect linkage) than the 5-allele marker assumed in the simulations.

Table 3 shows the estimated proportion of marker alleles shared by affected sib pairs in the core families and the associated one-sided *P* value for a test of >50% sharing, calculated by the SIBPAL program. None of the markers demonstrated sharing that was significantly >50%, indicative of genetic linkage. The *P* value for marker D6S291 (which produced a positive LOD score in the parametric analysis) was 0.12. Similarly, none of the markers demonstrated significantly <50% sharing in affected-unaffected pairs of siblings, which would also be indicative of linkage (results not shown).

Linkage/Association Analysis

Table 4 presents the results of nonparametric APM analysis; *P* values are shown for analyses using published and parental marker allele frequencies, with the three different methods of weighting allele frequencies. None of the markers showed significant linkage/association with either published or parental marker frequencies when no weighting was used. When weighting of rarer alleles was used, D6S299 and TNFB produced significant results, but only with published frequencies; *with parental marker allele frequencies, the significance of these results disappeared* (table 4).

Results of analysis using SIMIBD are presented in table 5. None of the markers produced significant evidence of linkage/association using either published or parental marker allele frequencies.

Association Analysis

Table 6 shows the *P* values from AFBAC association analysis (both simplex and multiple sibs analysis) for all markers. None of the results were statistically significant.

Marker Allele Frequencies

Since the significance of results of APM analyses for markers D6S299 and TNFB sometimes differed, depending on whether published or parental marker allele frequencies were used in the analyses, it might be informative to compare the marker allele frequency dis-

Table 4

APM *P* Value Using Three Weights

Marker	Weight[a]	Published Allele Frequencies	Parental Allele Frequencies
D6S299	(1)	.902	.731
	(2)	.000	.348
	(3)	.000	.464
D6S105	(1)	.999	.917
	(2)	.962	.952
	(3)	.587	.815
TNFB	(1)	.177	.862
	(2)	.056	.767
	(3)	.000	.602

[a] (1) $p = 1$ (no weight); (2) $1/\sqrt{p}$; (3) $1/p$ (Weeks and Lange 1988).

Table 5

SIMIBD *P* Values

Marker	Published Allele Frequencies	Parental Allele Frequencies
D6S299	.193	.574
D6S105	.663	.757
TNFB	.480	.660

tributions from these two sources. presents this comparison for D6S299, D6S105, and TNFB.

Discussion

Chromosome 6 Linkage

Although two research groups have reported a dyslexia-predisposing locus on chromosome 6p23–p21.3, we found no evidence for a locus predisposing to PCD (the most common type of dyslexia) in that chromosomal region in our large data set. Analyzing the same chromosome 6p markers reported to be linked in previous studies, we could find no evidence for linkage, using either LOD score or affected-sib-pair methods; for linkage/association, using the robust SIMIBD method; or for association, using family-based methods. Simulation studies showed that our pedigrees have excellent power ($\geqslant$90%) to detect highly suggestive evidence for linkage (LOD score >2) of a major dominant or recessive PCD locus, even if it is present in only half of the families and is only near rather than right at a tested marker (within 5% recombination). These results suggest that, if a dyslexia-predisposing locus does exist on chromosome 6p, it may be relevant to a subtype of dyslexia that was not well represented in our sample.

Our families were ascertained through probands attending schools for learning disabled children, but families entered the study only if a pair of siblings demonstrated impairment in phonological coding skills, whereas both Cardon et al. (1994) and Grigorenko et al. (1997) selected families on the basis of a more general phenotype (reading disability). Grigorenko et al. (1997) performed linkage analysis using subphenotypes defined by specific tests and found linkage of phonological *awareness* to chromosome 6p. They postulate that phonological awareness is a more "molecular" phenotype than phonological coding (Grigorenko et al. 1997, p. 29). Presumably this means that phonological awareness is a more basic defect and that all individuals deficient in phonological coding would also be deficient in phonological awareness, although the reverse would not be true (producing a weak correlation between the two traits). For example, additional genetic factors may be required to produce phonological coding deficits in a person already genetically disposed to phonological awareness problems. If this is so, then testing for linkage to a phonological coding phenotype should also detect genes involved in phonological awareness (in the LOD score analysis, reduced penetrance would allow individuals to possess an abnormal genotype for phonological awareness but still have a normal phonological coding phenotype). Thus, our analysis of linkage to PCD should also have detected any loci contributing to phonological awareness, yet we found no evidence for linkage to chromosome 6p.

We have data on phonological *awareness* from only one test (the Auditory Analysis Test, AAT). In our subjects, phonological coding and phonological awareness are significantly correlated ($r = 0.64$, $P < .0001$). Grigorenko et al. (1997) also reported a significant but weaker correlation between these two traits in their subjects ($r = 0.41$, $P < .05$). Formal LOD score analysis of linkage between phonological awareness (based on the AAT alone) and 6p markers in our families revealed no significant or suggestive scores (data not shown).

Inconsistent Results with APM Method

Using the nonparametric APM, we detected significant evidence for increased marker allele sharing in affected individuals (reflecting either linkage or association) with D6S299 and TNFB, but only when using published marker allele frequencies and employing weighting of rarer alleles. *Results were not significant, either with or without weighting, when marker allele frequencies estimated from parents* (*two per pedigree*) *were used*. It is well known that the APM approach is highly sensitive to the marker allele frequencies used in the analysis (e.g., Babron et al. 1993; Van Eerderwegh et al. 1993), and our results clearly demonstrate that sensitivity. shows that there are not large differences between allele frequency distributions that produce highly significant results and those that produce nonsignificant results: for example, compare the published and parental frequency distributions for TNFB, which gave *P* values of .000 and .602, respectively, with weighting method 3. One could

Table 6

AFBAC Association Analysis *P* Values

Marker	Simplex Analysis	Multiple Sibs Analysis
F13A1	.27	.67
D6S89	.64	.56
D6S299	.32	.15
D6S105	.60	.65
TNFB	.62	.36
D6S291	.66	.42
GLP1R	.50	.62

argue that the significant APM results in our study were created primarily by association rather than by linkage and that, when parental allele frequencies were used (estimated from parents of dyslexic children, some of whom were dyslexic themselves), the ability of the APM method to detect this association was weakened. However, the following should be noted: (1) no significant APM results were found with published allele frequencies when no allele weighting was used, and (2) there was no evidence for association when a method specifically designed to detect association in nuclear family data was used. We suggest that the APM method should be used only with great caution, and, if the APM method is used at all, it is imperative to use marker allele frequencies estimated directly from the study material.

The SIMIBD approach was developed partly to avoid the sensitivity of APM to specified marker allele frequencies (Davis et al. 1996). Like APM, it is a nonparametric method for testing whether affected relatives share marker alleles more often than expected by chance, but the statistic is based on simulating a null distribution conditional on marker genotypes of unaffected persons. Application of this method produced no significant evidence for linkage/association between PCD and the chromosome 6p markers with either published or parental marker allele frequencies. These SIMIBD results confirm our suspicion that our significant APM results were spurious, created by use of inappropriate published marker allele frequencies, with weighting of rarer alleles compounding the problem. Similar comments might apply to the significant chromosome 6p linkage obtained by Grigorenko et al. (1997) with APM analysis but, interestingly, not with LOD score analysis using either dominant or recessive models. Although they state that they estimated marker allele frequencies from their data (six pedigrees), how this was done is unclear. Theoretical investigations have suggested that LOD score analysis generally has greater power to detect linkage than nonparametric methods (e.g., APM), particularly if both dominant and recessive genetic models are tested (Goldin and Weeks 1993; Greenberg et al. 1996). Thus, it is surprising that Grigorenko et al. (1997) did not also find significant evidence for linkage using LOD score analysis.

In conclusion, we cannot confirm previous reports of linkage between dyslexia and chromosome 6p. It is possible that the earlier studies were enriched for subtypes of dyslexia not well-represented in our sample (because of either chance or varying ascertainment criteria); however, it is also possible that some of the significant results of previous studies were due to use of the APM program, which is extremely sensitive to marker allele frequencies specified in the analyses. Further research is required to determine the reason for the conflicting results.

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Electronic-Database Information

URLs for data in this article are as follows:

Cedar Genetics, http://cedar.genetics.soton.ac.uk (for relative map locations of markers used)
Généthon, http://www.genethon.fr (for relative map locations of markers used)
Genome Database, http://www.gdb.org (for published marker allele frequencies used)
Marshfield Center, http://www.marshmed.org/genetics/ (for relative map locations of markers used)

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