Biol Psychiatry. Author manuscript; available in PMC 2018 January 02.

Published in final edited form as:

Biol Psychiatry. 2009 August 15; 66(4): 368–375. doi:10.1016/j.biopsych.2009.02.016.

Association of Attention-Deficit/Hyperactivity Disorder with a Candidate Region for Reading Disabilities on Chromosome 6p

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Abstract

Background—Reading disabilities (RD) and attention-deficit hyperactivity/disorder (ADHD) are two common childhood disorders that co-occur by chance more often than expected. Twin studies and overlapping genetic linkage findings indicate that shared genetic factors partially contribute to this comorbidity. Linkage of ADHD to 6p, an identified RD candidate locus, has previously been reported, suggesting the possibility of a pleiotropic gene at this locus. RD has been previously associated with five genes in the region, particularly *DCDC2* and *KIAA0319.*

Methods—To test whether these genes also contribute to ADHD, we investigated markers previously associated with RD for association with ADHD and ADHD symptoms in a sample of families with ADHD (n = 264). Markers were located in two subregions, *VMP/DCDC2* and *KIAA0319/TTRAP.*

Results—Across all analyses conducted, strong evidence for association was observed in the *VMP/DCDC2* region. Association was equally strong with symptoms of both inattention and hyperactivity/impulsivity, suggesting that this locus contributes to both symptom dimensions. Markers were also tested for association with measures of reading skills (word identification, decoding); however, there was virtually no overlap in the markers associated with ADHD and those associated with reading skills in this sample.

Conclusions—Overall this study supports a previous linkage study of ADHD indicating a risk gene for ADHD on 6p and points to *VMP* or *DCDC2* as the most likely candidates.

Keywords

ADHD; genetic association; pleiotropic locus; RD

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The authors report no biomedical financial interests or potential conflicts of interests.

Supplementary material cited in this article is available online.

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood disorder that occurs in approximately 5% of the population and is characterized by developmentally disproportionate levels of inattention, impulsivity, and hyperactivity (1). It often co-occurs with reading disabilities (RD), another common disorder of childhood in both clinical (2, 3) and population-based (4, 5) samples. RD is a specific learning disability that occurs in 3%–6% of the population and is characterized by difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities. These difficulties occur despite adequate cognitive abilities and effective educational opportunities (International Dyslexia Association, 2002; http://www.interdys.org). In samples selected for ADHD, the rate of comorbid RD is between 25% and 40% (3), whereas in samples selected for RD, the rate of comorbid ADHD ranges from 15% to 26% (6).

Four competing hypotheses have been proposed to explain the comorbidity of RD and ADHD. The first proposed cross-assortative mating between individuals with either disorder (7). The second, the phenocopy hypothesis, suggested that individuals with the primary disorder could appear to exhibit symptoms of the secondary disorder because of etiologic influences of the primary disorder (8). The third hypothesis suggests that the comorbidity is a distinct subtype, with unique patterns of neuropsychological correlates (9). Thus far, additional studies have not found support for these hypotheses (5,9–11) . The last hypothesis suggests that common genetic factors contribute to this observed comorbidity (5, 12), a notion that has been supported by twin studies that estimate the bivariate heritability of RD and ADHD to range from .15 to .47 (12–15). When ADHD is subdivided into its symptom dimensions, twin studies also predict a stronger relationship between RD and symptoms of inattention (IA) compared with symptoms of hyperactivity/impulsivity (HI) (12). This is mirrored in the estimates of bivariate heritability, which are higher for IA (.39–.60) than for HI (.05–.35) (12, 14). Furthermore, genetic correlations between IA and reading discrepancy (.72), orthographic choice (.71), and phoneme awareness (.41) (14), suggest that these reading component processes and inattention will share a subset of susceptibility genes. Genetic correlations for measures of HI and RD were not as high (.37 and .40) (14).

Given this evidence for overlapping heritability, several studies have begun to investigate the genetic relationship between RD and ADHD. Results from linkage studies of RD and from genome scans of ADHD have indicated several regions that overlap. Notably, two regions, 6q12–q14 and 15q, previously identified in linkage studies of RD (16–22), were identified in genome scans of sibling pairs affected with ADHD (23, 24). Overlapping loci on 16p, 17p, 10q, 14q32, 13q32, and 20q11 have also been suggested by additional studies (24–26). Specific candidate genes associated with RD or ADHD have been investigated for linkage or association in the other disorder, for which supporting evidence has been found. These include the region of the *DYX1C1* (EKN1) locus in the RD linkage region on 15q (27, 28) and *DRD4* on 11p (29, 30).

The most studied chromosomal region in conjunction with RD has been 6p21–22, where multiple studies have found linkage (16, 18, 31–37). Willcutt and colleagues (38) investigated linkage of the ADHD phenotype to the RD locus on chromosome 6p in a sample of sibling pairs ascertained for RD. Results from their study showed linkage to ADHD between markers D6S276 and D6S105 (38) (Figure 1). These results remained

significant for both markers when the reading phenotypes were regressed and linkage of the residual scores was analyzed, suggesting that linkage to ADHD was not a consequence of reading problems (38). In addition, evidence for significant bivariate linkage to D6S105 was found, suggesting that the 6p locus was pleiotropic for both RD and ADHD (38). The linkage results of Willcutt and colleagues for ADHD, and the previous linkage studies of RD implicated a broad region on 6p containing multiple genes; thus, it was not clear which of the genes in the region would contribute to RD and/or ADHD, and further fine mapping was required.

The first study to fine map the 6p region for RD identified associated markers in five candidate genes; vesicular membrane protein, p24 (VMP; recently named *Neurensin 1, NRSN1*), doublecortin domain containing-2 (DCDC2), *KIAA0319,* TRAF and TNF associated protein (TTRAP) and a member of the thioesterase superfamily of genes (THEM2) (34) (Figure 1). Additional follow-up studies have since been conducted, and results have converged on *KIAA0319* (36, 39–41) and *DCDC2* (42, 43) as the two most likely RD candidates at this locus. We have previously investigated association of markers in these five genes with RD. Results from our study also support a role for *KIAA0319,* however, some evidence for association was also found with single markers in *VMP,* the distal neighbor of *DCDC2* (Figure 1) (44). No evidence for association with *DCDC2* was identified.

The most significant markers from the bivariate linkage study of Willcutt *et al.* (38), D6S276 and D6S105, flank the current RD candidate region on 6p, with D6S276 lying proximal to *VMP* and within *DCDC2* (Figure 1). The other RD candidate, *KIAA0319,* is located less than .5 Mbp centromeric to *DCDC2.* On the basis of the genetic overlap between these two disorders and the convergence of bivariate linkage to a region surrounding these RD candidate genes on 6p (38), we hypothesized that these specific genes might also be associated with ADHD, particularly the IA symptoms. Therefore, this investigation focused on markers in two regions, *VMP/DCDC2* and *KIAA0319/TTRAP,* previously reported to be associated with RD either individually or as haplotypes. Specifically, we investigated the markers and the haplotypes of rs793862–rs807701 in *DCDC2* (42, 43), rs4504469–rs2038137-rs2143340 in *KIAA0319* and *TTRAP* (36,40,41), and rs4504469–rs6935076 in *KIAA0319* (39–41). The two markers in *DCDC2* were strongly associated with RD in two independent samples from Germany (42,43). The three markers that were used to derive the second set of haplotypes in *KIAA0319* and *TTRAP* were first associated with RD in samples from the United Kingdom and the United States (36,40,41). Association of this set of haplotypes with RD was also identified in two studies using population-based samples (41,45). The next set of haplotypes comprising two markers in *KIAA0319* were first associated with RD in an additional sample from the United Kingdom (39–41). An additional two markers in *VMP,* rs3178 and rs3829810, and two in *KIAA0319,* rs12194307 and rs12213672, were also investigated. The first was associated with RD in our previous study (44) and, along with the second marker, tagged variation greater than or equal to 10% within a haplotype block in *VMP* (http://www.hapmap.org; Rel22/phaseII April 2007) (46). The latter two along with the four previously associated markers in *KIAA0319* and *TTRAP* cover a region of high linkage disequilibrium (LD) across these two genes in which 11

single nucleotide polymorphisms (SNPs) associated with RD in previous studies are located (36,39–41,44).

The association of ADHD and ADHD symptoms was investigated using a sample of families comprising probands meeting DSM-IV criteria for one of the three DSM-IV subtypes of ADHD (28,47,48).

Methods and Materials

Study Sample

The sample consisted of 264 nuclear families from the Toronto area, which includes 264 probands and 55 siblings between the ages of 7 and 16 selected on the basis of an ADHD diagnosis (described below). Of these, 192 were two- parent families, 157 with one child, 55 with two children, and two with three children. There were also 72 single-parent families, 55 with one child, 16 with two children, and one with three children. Ninety percent of the participants described their ethnicity as “European,” and the other 10% were of “other” or “mixed” backgrounds. These included Chinese, African, Indian, and Native American (47). Although this sample is not entirely ethnically homogenous, the association design employed here is robust to population stratification because it evaluates transmission of marker alleles, while the untransmitted alleles within each family are used as internal controls (49).

Diagnostic Assessment

Subjects were recruited following referral to the Child Development and Neuropsychiatry Clinics at the Hospital for Sick Children in Toronto. Children were included in the study if they met DSM-IV criteria for one of the three DSM-IV ADHD subtypes (IA, HI, and combined). The diagnosis of ADHD was based on semi-structured interviews with parents (Parent Interview for Child Symptoms [PICS-IV]) (50) and teachers (Teacher Telephone Interviews [TTI-IV]) (51), with additional information on behavior and academic skills collected from standardized questionnaires and assessments: Conners Parent and Teacher Rating Scales—Revised (52); Ontario Child Health Survey Scales—Revised (53); Wide Range Achievement Test—3rd revision (WRAT) (54); Woodcock Reading Mastery Tests—Revised (WRMT-R) (55); Clinical Evaluation of Language Fundamentals, 3rd ed. (56); Children’s Depression Inventory (57); and Children’s Manifest Anxiety Scale (58). All children were free of medication for 24 hours before assessment. The distribution of DSM-IV ADHD subtypes was as follows: 14% were predominantly HI, 27% were IA, and 59% were combined. Information on ADHD symptom dimensions from the PICS-IV and TTI-IV were used in the quantitative analyses. In this sample, only 31 individuals met criteria for RD on the basis of criteria used in a study of RD that identified individuals who fell, on average, in the lower 5% of the population in reading skills (27). Therefore, a categorical analysis of RD was not conducted in this sample. Measures ascertained from the WRAT 3 Reading, WRMT Word ID, and WRMT Word Attack subtests were used in the quantitative analyses of reading. Descriptive statistics for this sample can be found in Table 1.

Subjects were excluded if they showed evidence of neurological or chronic medical illness, bipolar affective disorder, psychotic symptoms, Tourette syndrome, or chronic multiple tics. Children were also excluded if they scored below 80 on both the Performance and Verbal Scales of the Wechsler Intelligence Scale for Children III (59).

Isolation of DNA and Marker Genotyping

DNA was extracted directly from blood lymphocytes using a high-salt extraction method (60). We investigated single nucleotide polymorphism (SNP) markers in the genes for *VMP, DCDC2,* and in the 5′ regions of the genes for *KIAA0319* and *TTRAP* (Figure 1). The specific markers were selected from prior published studies and association findings for RD as well as measures of reading in our previous study of RD (44) The assays employed here were either predesigned (Assay-on-Demand by Applied Biosystems, Foster City, California; see Table S1A in Supplement 1) or designed from flanking sequence (UCSC database builds 33–35; Assay-by-Design Table S1B in Supplement 1). Genotyping was conducted with the ABI 7900-HT Sequence Detection System (Applied Biosystems) using the TaqMan 5′ nuclease assay for allelic discrimination and the end point analysis mode of SDS software package version 2.0 (Applied Biosystems). The G/T polymorphism rs2038137 was genotyped using a standard polymerase chain reaction (PCR; annealing temp 58°C) followed by an analysis with the restriction enzyme BstUI (New England Biolabs, Beverly, Massachusetts). PCR primer sequences were as follows: *KIAA0319*-8137 F: GGTTGGGAAAAGACACTCAA and *KIAA0319*-8137 R: GACGACGAGGAGGAACAAGT. The more frequent allele, *G,* was cut by the enzyme, while the other allele, *T,* was not cut.

Statistical Analysis

Following the genotyping, all markers were tested for Mendelian errors, crossovers, and Hardy-Weinberg equilibrium using Merlin (61). For all 10 SNP assays, genotyping success rates ranged from 99% to 100%. For the single marker categorical analysis, the TDT statistic was calculated using the extended TDT (ETDT) program (62). *p* values from the TDT analysis of all 10 SNP were corrected using a permutation test, running 1000 permutations in UNPHASED (63). For each permutation, transmission status of the parental haplotypes was randomized and the minimum *p* value was compared with the minimum *p* value of all markers from the original analyses. This provides a correction over all markers in the analyses (63). Haplotype transmission for ADHD defined as a categorical trait was analyzed using the TRANSMIT program (64). For these analyses, the *p* values are only reported for haplotypes with frequencies greater than .10, and those with a frequency of less than 10% were included in the Global chi-square test. Analysis of the quantitative measures of IA and HI as reported by both parents and teachers was carried out using the Family Based Association Test (FBAT) program and the HBAT component for the quantitative analysis of haplotypes (65). The null hypothesis (H_o) for the FBAT analysis was no linkage and no association. The following offsets based on means from a healthy screened control sample were used to mean center traits (66): Parent IA = 1.45, Parent HI = 1.05, Teacher IA = 1.1, Teacher HI = .74.

Results

Ten markers in *VMP, DCDC2, KIAA0319*, and *TTRAP* were tested for association with ADHD using a single-marker categorical analysis (n = 264 affected children). Both markers in the gene for *DCDC2* were significantly associated with ADHD. These were rs793862 (χ^2 = 7.049, p = .008) and rs807701 (χ^2 = 16.990, p = .00004; Table 2). In the gene for *VMP,* significant evidence for association of ADHD was observed with rs3829810 (χ^2 = 5.896, p = .015) and rs3178 (χ^2 = 5.586; p = .018; Table 2). Single markers in the genes for *KIAA0319* and *TTRAP* were not associated with ADHD (Table 2). The p values for all 10 markers were corrected for multiple testing using 1000 permutations (63). The corrected p value was .002.

Twin studies of ADHD symptom dimensions have identified shared and independent genetic factors contributing to both the IA and the HI dimensions, indicating that risk genes may contribute to both or either of the dimensions (67). On this basis, we also analyzed both symptom dimensions separately as quantitative measures. Following the prediction from twin studies of a stronger genetic relationship between IA and RD (12), we hypothesized that genes contributing to RD were more likely to be associated with the IA symptoms. Because these were secondary analyses based on our initial findings from the TDT, a second correction for multiple testing was not applied.

A single-marker quantitative analysis showed that both markers in *DCDC2,* rs793862 and rs807701, were significantly associated with parent-reported IA (Z = 2.374, p = .018; Z = 4.016, p = .00006) and HI (Z = 2.407, p = .016; Z = 3.746, p = .00018) symptoms (Table 3). The marker rs793862 was also associated with teacher-reported IA (Z = 2.127, p = .033). Similarly, rs807701 was associated with both teacher-reported IA (Z = 3.600, p = .0003) and HI (Z = 3.013, p = .003). In *VMP*, rs3829810 was significantly associated with both parent-reported IA (Z = 2.434, p = .015) and HI (Z = 2.535, p = .011) symptoms (Table 3). Neither marker in *VMP* was associated with teacher-reported symptoms (Table 3). In the *KIAA0319/TTRAP* region, rs12194307 in *KIAA0319* was significantly associated with both parent-reported IA (Z = 3.025; p = .002) and HI (Z = 2.175, p = .030) symptoms. This marker was also significantly associated with teacher IA (Z = 2.644, p = .008) and HI (Z = 2.586, p = .010) (Table 3).

Analyses of association of haplotypes with ADHD defined as a categorical trait were also conducted. Markers were grouped as haplotypes on the basis of previous studies of RD: rs793862–rs807701 in *DCDC2* (42,43), rs3829810–rs3178 in *VMP* (44), rs4504469–rs2038137–rs2143340 in *KIAA0319* (36,41), rs4504469–rs6935076 in *KIAA0319* (39,44), and rs4504469–rs12194307–rs12213672–rs6935076–rs2038137–rs2143340 in *KIAA0319/TTRAP* (44) In *DCDC2*, two haplotypes, G-T, and A-C, were significantly associated with ADHD (χ^2 = 9.248, p = .002 and χ^2 = 10.172, p = .001, respectively, global p = .002, 3 df) (Table 4). In *VMP*, the G-A haplotype was significantly associated with ADHD (χ^2 = 5.245, p = .022), although the global test was not significant (p = .069; Table 4). All three groups of haplotypes across *KIAA0319* and *TTRAP* were not associated with ADHD in the categorical analyses of haplotypes (data not shown).

These haplotypes were also tested for association with quantitative measures of ADHD (Table 5). Haplotypes consisting of the two markers in *DCDC2* were significantly associated with both parent-reported IA (G-T: $Z = -2.978$, $p = .003$; A-C: $Z = 3.976$, $p = .00007$: A-T: $Z = -2.519$, $p = .012$) and HI (G-T: $Z = -2.948$, $p = .003$; A-C: $Z = 3.964$, $p = .00007$; A-T: $Z = -2.080$, $p = .038$; Table 5). Similarly, haplotypes in *DCDC2* were also associated with teacher-reported IA (G-T: $Z = -2.705$, $p = .007$; A-C: $Z = 3.498$, $p = .0005$; A-T: $Z = -2.123$, $p = .034$) and HI (G-T: $Z = -2.427$, $p = .015$; A-C: $Z = 2.752$, $p = .006$; Table 5). When investigated for association with parent-reported ADHD symptoms, haplotypes consisting of the two markers in *VMP* were significantly associated with IA (G-A: $Z = -2.390$, $p = .017$; A-G: $Z = 2.092$, $p = .036$) and HI (A-G: $Z = 2.099$, $p = .036$) symptoms (Table 5). These haplotypes in *VMP* were not associated with teacher-reported IA or HI symptoms. No significant evidence for association was found for any haplotypes of markers in the *KIAA0319/TTRAP* regions in the quantitative analyses (data not shown).

Because these genes have previously been implicated as quantitative trait loci for measures of reading, we also analyzed single-word reading (WRMT—Word ID and WRAT—3 Reading) and phonological decoding (WRMT Word Attack) using quantitative analyses. Only rs12194307 in *KIAA0319* was modestly associated with phonological decoding ($Z = -2.513$, $p = .012$) (Table 3). All other markers, including those in *VMP*, *DCDC2*, and *TTRAP* were not associated with the reading components tested (Table 3).

Discussion

Twin studies have provided estimates of both bivariate heritability and genetic correlations for RD and symptoms of ADHD, particularly inattention, suggesting that some genes will be shared between the two. However, how exactly this manifests in gene function is unknown. That 6p22, particularly *DCDC2* and/or *KIAA0319* is an RD susceptibility locus has been well supported (36,39–43). There has also been some support for *VMP* (34,44). A previous study by Willcutt and colleagues also linked ADHD to 6p22 (38). The most parsimonious explanation for these findings for both ADHD and RD (38) would be the presence of a pleiotropic gene. To test this hypothesis, we focused on markers previously associated with RD to investigate whether they would also be associated with ADHD and its symptom dimensions.

Our study shows strong association of markers in the 6p22 region with ADHD and the ADHD symptom dimensions, supporting the linkage study of Willcutt and colleagues. However, the determination of the specific ADHD candidate gene is not clear at this time. Association was much stronger in the *DCDC2/VMP* region compared with the *KIAA0319/TTRAP* region. Within the *DCDC2/VMP* region, the markers rs793862 and rs807701 in *DCDC2* were most strongly associated with ADHD across all analyses conducted. Markers in *VMP* were also significantly associated with ADHD, albeit not as strongly or consistently as markers in *DCDC2*. In the *KIAA0319/TTRAP* region, one marker in *KIAA0319* was associated with symptoms of IA and HI in the single-marker quantitative analysis. However, there was no association with this or any marker in any of the other analyses conducted, making *KIAA0319* the weakest of all three candidates for ADHD.

In the *VMP/DCDC2* region, it is unsurprising that association findings extend across both genes given that they are adjacent and in a region of high LD. We previously conducted a detailed analysis of intermarker LD across 44 markers in *DCDC2*, *VMP*, *KIAA0319, TTRAP,* and *THEM2* in an independent study sample from Toronto selected for probands with reading difficulties (44). Intermarker LD was then compared with LD across this region in the HapMap sample. In both samples, high levels of LD were found between the 11 markers tested in *VMP* and the 8 markers tested in *DCDC2.* In addition, two out of three previously published studies of RD in the region that found support for *DCDC2* also showed some evidence for association of markers in *VMP* with RD (34,42,43), suggesting that markers in both genes could be in LD with RD risk conferring DNA variants. Overall, the high level of LD between markers in this region will make it difficult to determine both the true candidate gene and the location of causal variants.

Twin studies consistently predict a stronger genetic relationship between RD and IA (12,14). Because 6p22 is an established RD locus, we hypothesized a stronger association with IA. Therefore, it was surprising when we observed equally strong association of markers with both the HI and IA symptom dimensions in the quantitative analyses. A recent twin study showed that although genetic correlations between RD and IA symptoms were high, genetic correlations between RD and HI were not entirely absent (14). This suggests that some RD loci contribute to HI in addition to IA, which appears to be the case on 6p. This study is the first at this locus to partition the ADHD phenotype into its symptom dimensions.

Discrepancies among informants of ADHD behavior have been extensively documented, with twin studies indicating evidence for a common genetic factor underlying parent and teacher ratings of symptoms, together with additional, informant-specific genetic influences (68,69), supporting our analyses of the symptoms separately by informant. However, for the analyses here, the results are fairly consistent between parents' and teachers' ratings of ADHD symptoms, with markers in *DCDC2* associated with ADHD symptoms as reported by both informants. The associated marker in *VMP,* rs3829810, was significant for parent report of both IA and HI but not significant for teacher report of these symptoms. However, there were trends in the same direction for the teacher-reported symptoms for the same alleles.

We also tested markers for association with measures of reading skills because these markers have all been associated with RD, or quantitative measures of reading, in previous studies. All four markers in *VMP* (rs3829810, rs3178) and *DCDC2* (rs793862 and rs807701), associated with ADHD were not associated with the RD measures tested. The same alleles of rs793862 and rs807701 in *DCDC2* have been associated with RD both individually and as a haplotype in two independent German samples (43). However, these results were not replicated in two additional studies of three independent RD samples (40,44). Markers in *VMP* have also been associated with RD (34,44), including rs3178 (44), which was associated with ADHD in our study. However, in both of those studies, support for either *DCDC2* (34) or *KIAA0319* (44) was stronger. A single marker in *KIAA0319* in our study showed marginally significant association with phonological decoding (WRMT Word Attack). This marker was also associated with IA and HI symptoms in the single-marker quantitative analysis but not the other analyses conducted. Results from quantitative analyses

should be interpreted cautiously, however, because they can be affected by factors that include the variance and the reliability of the phenotypic measure (70). In addition, only 31 individuals from our ADHD sample also met the criteria for a diagnosis of RD. Therefore, there might not have been enough power in this sample for this particular analysis, especially if this locus contributes to more severe RD as has been previously shown (36,39–43). Thus far, there is no clear and consistent overlap for association of the same markers with symptoms of both ADHD and reading skills in the same sample. Instead, there is evidence of strong association with RD from previous studies (36,39–43) and association with ADHD in our study. Therefore, there is currently not enough evidence to single out one specific pleiotropic gene for ADHD and RD on 6p.

In conclusion, the results from this study suggest that in addition to RD, the 6p22 locus also contributes to ADHD, supporting the 2002 study of Willcutt *et al.* (38). Our data narrow the search area by suggesting that the causal variants for ADHD might be found in the *VMP/DCDC2* region. These data also suggest that the causal variants for ADHD within this region contribute to both IA and HI symptoms. Overall, additional studies with independent samples selected for RD, ADHD, and both disorders will be required before we can assess whether these genes are pleiotropic for both disorders.

Acknowledgments

We thank Abana Nathaniel for help with assessment of families. This work was supported by the Canadian Institute of Health Research (Grant Nos. MOP-36358, MT14336, MOP-14334 to CLB) and a graduate student fellowship from the Hospital for Sick Children Research Training Centre (JMC). We thank the children and families who participated in this study.

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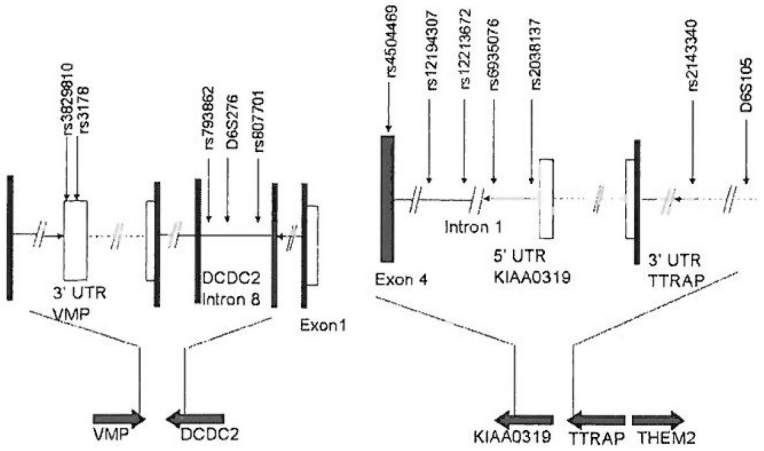

Figure 1.

Location of markers investigated in the reading disability (RD) candidate region on 6p. Schematic showing the ~ 589-kb region on chromosome 6p, with the five candidate genes, *VMP, DCDC2, KIAA0319, TTRAP,* and *THEM2,* drawn as thick horizontal arrows at the bottom of the figure. Portions of the 3′ region of *VMP* and *DCDC2,* 5′ region of *KIAA0319,* and the 3′ region of *TTRAP* have been expanded to show the location of markers genotyped for this study (vertical arrows). The two markers in *VMP* are 900 bp apart. The marker rs3178 in *VMP* is 59.6 kb away from rs793862 in *DCDC2.* The region between rs793862 and rs807701 across intron 8 in *DCDC2* is 66.6 kb in length. The region across *KIAA0319* and *TTRAP* is 70.2 kb in length. The marker D6S105 is approximately 3.1-Mbp away from rs2143340, toward the centromere of chromosome 6. Untranslated regions (UTR) of these genes are drawn as shorter, clear boxes, and coding exons are depicted as longer, filled boxes.

Table 1

Descriptive Statistics for the Attention-Deficit/Hyperactivity Disorder Sample (n = 319)

Measure	Mean	SD	Skewness	Kurtosis
Parent inattention (PICS)	5.20	2.44	−.49	2.59
Parent hyperactive/impulsive (PICS)	4.86	2.74	−.22	1.95
Teacher inattention (TTI)	4.64	2.53	−.42	2.18
Teacher hyperactive/impulsive (TTI)	3.51	2.75	.24	1.80
WRAT3 Read	97.23	14.31	−.25	3.42
WRMT Word ID	95.58	14.43	−.67	3.84
WRMT Word Attack	94.15	13.4	−.59	3.18

PICS, Parent Interview for Child Symptoms; TTI, Teacher Telephone Interviews; WRAT3, Wide Range Achievement Test—3rd revision; WRMT, Woodcock Reading Mastery Tests.

Table 2

Single-Marker TDT Analysis for Markers in the *VMP/DCDC2* and *KIAA0319/TTRAP* Regions in the Attention-Deficit/Hyperactivity Disorder Sample

Gene	Marker	Allele	Frequency	Transmissions	Nontransmissions	χ^2	*p* Value
VMP	rs3829810	A	.25	97	66	**5.896**	**.015**
		G	.75	66	97		
	rs3178	*G*	.49	134	98	**5.586**	**.018**
		A	.51	98	134		
DCDC2	rs793862	A	.35	99	65	**7.049**	**.008**
		G	.65	65	99		
	rs807701	*C*	.35	128	70	**16.990**	**.000**[a]
		T	.65	70	128		
KIAA0319	rs4504469	A	.34	114	112	.018	.893
		G	.66	112	114		
	rs12194307	*T*	.83	51	40	1.330	.249
		A	.17	40	51		
	rs12213672	*T*	.95	16	9	1.960	.162
		G	.05	9	16		
	rs6935076	A	.37	101	95	.184	.668
		G	.63	95	101		
	rs2038137	*T*	.30	93	81	.828	.363
		G	.70	81	93		
TTRAP	rs2143340	*G*	.16	61	57	.136	.712
		A	.84	57	61		

[a] $p = .000038$. corrected $p = .002$, over all 10 markers.

Table 3

Single Marker Quantitative Analyses of Attention-Deficit/Hyperactivity Disorder Symptom Counts and Reading Components

Gene	Marker	Allele	Freq	*Z*	*P*	*Z*	*P*	*Z*	*P*
Parent-Reported Symptoms				*IA*		*HI*			
VMP	rs3829810	A	.25	2.434	**0.015**	2.535	**0.011**		
	rs3178	G	.50	1.619	0.105	1.299	0.194		
DCDC2	rs793862	A	.35	2.374	**0.0176**	2.407	**0.016**		
	rs807701	C	.35	4.016	**0.00006**	3.746	**0.0002**		
KIAA0319	rs4504469	A	.34	−1.349	0.177	−0.344	0.731		
	rs12194307	T	.83	3.025	**0.002**	2.175	**0.030**		
	rs12213672	T	.95	1.430	0.153	1.093	0.274		
	rs6935076	G	.63	.304	0.761	−0.081	0.936		
	rs2038137	T	.30	.392	0.695	−0.550	0.582		
TTRAP	rs2143340	A	.84	.306	0.759	−0.656	0.512		
Teacher-Reported Symptoms				*IA*		*HI*			
VMP	rs3829810	A	.25	1.420	.156	1.847	.065		
	rs3178	G	.50	.751	.453	1.249	.212		
DCDC2	rs793862	A	.35	2.127	**.033**	1.905	.057		
	rs807701	C	.35	3.600	**.0003**	3.013	**.003**		
KIAA0319	rs4504469	A	.34	.122	.903	.408	.684		
	rs12194307	T	.83	2.644	**.008**	2.586	**.010**		
	rs12213672	T	.95	.951	.342	−.043	.966		
	rs6935076	G	.63	−.831	.406	−.449	.653		
	rs2038137	T	.30	.181	.856	−.186	.852		
TTRAP	rs2143340	A	.84	.626	.531	−.155	.877		
Reading Components				*WRAT 3 Reading*		*WRMT Word ID*		*WRMT Word Attack*	
VMP	rs3829810	A	.25	−713	.476	−.809	.419	−1.523	.128
	rs3178	G	.50	.458	.647	−.784	.433	−1.362	.173
DCDC2	rs793862	A	.35	.353	.724	−.276	.782	−.282	.778
	rs807701	C	.35	−.599	.549	−.039	.969	−1.336	.182
KIAA0319	rs4504469	A	.34	.942	.346	−.122	.903	−.732	.464
	rs12194307	T	.83	−1.026	.305	−1.709	.087	−2.513	**.012**
	rs12213672	T	.95	−.085	.932	1.731	.084	.525	.600
	rs6935076	G	.63	−.898	.369	−1.043	.297	.542	.588
	rs2038137	T	.30	−.009	.992	−.715	.474	−1.654	.098
TTRAP	rs2143340	A	.84	1.666	.096	1.771	.077	1.371	.170

Table 4

Categorical Analysis of Haplotypes in *VMP* and *DCDC2* in the Attention-Deficit/Hyperactivity Disorder Sample

Gene	Marker 1	Marker 2	Freq.	Observed	Expected	Var.(O-E)	χ^2 (1 *df*)	*p* Value
VMP	rs3829810	rs3178						
	G	A	.506	309.580	328.830	70.605	**5.245**	**.022**
	A	*G*	.247	171.860	162.480	49.019	1.795	1.180
	G	*G*	.245	166.470	157.540	50.954	1.564	.211
	A	A	.002	2.086	1.149	.489	***	***
DCDC2	rs793862	rs807701						
	G	*T*	.562	290.750	314.010	58.510	**9.248**	**.002**
	A	*C*	.251	161.750	140.310	45.207	**10.172**	**.001**
	G	*C*	.131	81.249	73.587	28.694	2.046	.153
	A	*T*	.055	26.249	32.093	12.687	2.692	***

VMP, global χ^2 test, on 3 degrees of freedom = 7.0785, $p = .069$. *DCDC2*: global χ^2 test, on 3 degrees of freedom = 15.397, $p = .002$.

Table 5

Quantitative Analysis of Haplotypes in *VMP* and *DCDC2* and Attention-Deficit/Hyperactivity Disorder

			Parent IA		Parent HI		Teacher IA		Teacher HI	
Haplotypes		**Freq**	***Z***	***P***	***Z***	***P***	***Z***	***P***	***Z***	***P***
VMP										
G	A	.51	−2.390	**.017**	−1.845	.065	−1.738	.082	−1.763	.078
A	G	.25	2.092	**.036**	2.099	**.036**	1.032	.302	1.557	.120
G	G	.24	.537	.591	−.004	.997	.711	.477	.513	.608
DCDC2										
G	*T*	.57	−2.978	**.003**	−2.948	**.003**	−2.705	**.007**	−2.427	**.015**
A	*C*	.25	3.976	**.00007**	3.964	**.00007**	3.498	**.0005**	2.752	**.006**
G	*C*	.13	.663	.507	.741	.459	.917	359	.951	.342
A	*T*	.05	−2.519	**.012**	−2.080	**.038**	−2.123	**.034**	−1.462	.144

HI, hyperactivity/impulsivity; IA, inattention.