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ORIGINAL ARTICLE

Dyslexia and *DYX1C1*: deficits in reading and spelling associated with a missense mutation

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The status of *DYX1C1* (C15q21.3) as a susceptibility gene for dyslexia is unclear. We report the association of this gene with reading and spelling ability in a sample of adolescent twins and their siblings. Family-based association analyses were carried out on 13 single-nucleotide polymorphisms (SNPs) in *DYX1C1*, typed in 790 families with up to 5 offspring and tested on 6 validated measures of lexical processing (irregular word) and grapheme–phoneme decoding (pseudo-word) reading- and spelling-based measures of dyslexia, as well as a short-term memory measure. Significant association was observed at the misssense mutation rs17819126 for all reading measures and for spelling of lexical processing words, and at rs3743204 for both irregular and nonword reading. Verbal short-term memory was associated with rs685935. Support for association was not found at rs3743205 and rs61761345 as previously reported by Taipale *et al.*, but these SNPs had very low (0.002 for rs3743205) minor allele frequencies in this sample. These results suggest that *DYX1C1* influences reading and spelling ability with additional effects on short-term information storage or rehearsal. Missense mutation rs17819126 is a potential functional basis for the association of *DYX1C1* with dyslexia.
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Introduction

Reading is a normally varying, heritable, neurodevelopmental trait.[1,2] Epidemiological studies suggest that dyslexia—severe difficulties in acquiring reading, unexplained by educational opportunity or general cognitive ability—affects 5–12% of school-age children.[3] Genetic studies suggest that this disorder is genetically complex, with at least a dozen genes having a major role in its development,[4] influencing the specific form of dyslexia[5] and underlying normal neurodevelopmental variation in reading and spelling.[6]

Chromosome 15 was the first linkage reported for dyslexia[7] and in the subsequent 20 years has been repeatedly confirmed (with some exceptions[8,9]), with the region of support moving to focus on 15q15–21.[6,10–16] *DYX1C1* is a 78-kb gene located in this region and first implicated as a dyslexia candidate following study of a Finnish family transmitting a chromosomal translocation at 15q21.[1] Sequence variation analyses suggested that two low-frequency polymorphisms were associated with dyslexia: rs3743205 in the regulatory region of the gene and rs61761345, creating a premature stop codon in the coding region.[1] Molecular-developmental support for *DYX1C1* as a gene affecting reading was provided from the finding that, in common with the three other candidate dyslexia genes, *DYX1C1* is involved in brain development, in particular in neuronal migration[17,18] and the formation of molecular layer ectopias[19] believed to underlie dyslexia.[20]

Despite the translocation and molecular-developmental evidence, and in contrast to *KIAA0319*[21,22] and *DCDC2*[23,24] on 6p22, *DYX1C1* has not been compellingly shown as affecting variation outside the Finnish families in which it was discovered.[4] A further limitation on our understanding is that, to date, no functional mutations have been confirmed for any of these four candidates. Finally, *KIAA0319* and *DCDC2* appear to have significant effects on normal variation in reading,[25,26] which has not been shown for *DYX1C1*.

Previous studies of *DYX1C1* have rendered mixed results. Wigg *et al.*[27] analyzed six single-nucleotide polymorphisms (SNPs) (rs2007494, rs3743205, rs3743204, rs11629841, rs692691 and rs61761345) in 148 young (aged 6–16 years) probands and their siblings and parents where available. This group found a significant effect of rs61761345, but in the reverse direction to that reported by Taipale *et al.*[1] Quantitatively, rs61761345 was related to measures of

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both regular and irregular word reading, as well as to rapid automated naming and nonword repetition. Wigg *et al*. also reported significant association for rs11629841 and for haplotypes involving this SNP (rs11629841/rs3743204 and rs11629841/rs692691) as well as for the rs3743205/rs61761345 haplotype reported by Taipale. Dahdouh *et al*.[28] examined the two markers (rs3743205 and rs61761345) reported by Taipale *et al*. and additional SNPs in the promoter (rs12899331, rs16787 and rs8043269 (the latter dropped at assay assessment)) and the coding region (rs3743204 and rs600753), a total of 8 SNPs in 366 family trios ascertained based on a $\geqslant 1$ s.d. spelling-ability discrepancy from that predicted from intelligence test scores (IQ). They report their most significant result being restricted to female trios ($n=66$), for a three-SNP haplotype spanning rs3743205/rs3743204/rs600753 (GGG, $P=0.006$). This may reflect a sex-limited gene effect, or the higher heritability of dyslexia in females.[29] The effect was mostly accounted for by an association with short-term memory, supporting the finding of Marino *et al*.[30] that the SNPs reported by Taipale may be related more to short-term memory than to dyslexia. Brkanac *et al*.[31] recently reported a nominally significant association of rs61761345 in a sample of 191 dyslexic probands, together with their parental and matched unrelated controls.

Scerri *et al*.[32] in a study of 1153 individuals from 264 families again reported a nominally significant association for the common (−3G/1249G rather than rare −3A/1249T) haplotype, where the 1249GT polymorphism is equivalent to rs6171345. As only orthographic choice (identifying the correctly spelled word in pairs such as sammon–salmon) showed significant association, among the additional phenotypes and SNPs tested, along with the opposite direction of association, these authors suggested that the study should be interpreted as a failure to replicate. Clear null findings have been reported by Cope *et al*.[33] and Meng *et al*.[23] Cope *et al*. genotyped the two significant markers from the original Finnish study and the marker rs11629841 reported by Wigg *et al*., but found no significant support for any of these markers in 247 UK Caucasian parent–proband trios ascertained based on 8- to 18-year-old probands with a reading delay of >2.5 years. Meng *et al*.[23] found no significant support for association at rs3743205 or rs61761345 in 522 individuals consisting of index cases from 150 nuclear families in the Colorado twin study, as well as parents and siblings where available. A further small ($n=57$) study also failed to find an association in Italian school children.[34] In modest samples, with high ancestral SNP frequencies, there are often few informative events. The power of these studies to detect the effects of very common SNPs accounting for 2% of variance is only modest. However, the results to date suggest that although *DYX1C1* is implicated as a candidate, rs3743205 and rs61761345 are at best a rare cause of reading disability,[21,23,32] perhaps specific to the Finnish family or a genetic background. Studies therefore turned to genes in nearby regions,[35] although no candidates have been identified to date,[36] and to the analyses of a small number of additional SNPs in *DYX1C1*, again without success to date.[37]

Thus, although *DYX1C1* may be a susceptibility gene for developmental dyslexia, the causal alleles are unknown. Here, we report the first study examining the association of polymorphisms in *DYX1C1* with normal variation in reading, examining association at the 2 coding SNPs reported by Taipale *et al*.,[1] and 11 additional tagging SNPs in *DYX1C1*. On the basis of our hypothesis that dyslexia represents the low tail of a population's reading-ability distribution, we expected to replicate and generalize the association of *DYX1C1* polymorphisms with normal reading ability in this large unselected sample.

Materials and methods

Subjects

Twins were initially recruited from primary schools in the greater Brisbane area, by media appeals and word of mouth, as part of ongoing studies of melanoma risk factors and cognition.[38,39] Data were also gathered from non-twin siblings of twins, with families comprising up to five siblings (including twins). There were two waves to this study: the first in which reading and spelling measures were collected and the second in which language measures (including short-term memory) were added to the existing test battery. Exclusion criteria were parental report of significant head injury, neurological or psychiatric illness, substance abuse or dependence, or current use of psychoactive medication in either twin.

Data were available for 284 dizygotic twin pairs and a further 164 dizygotic families with at least one additional non-twin sibling (203 siblings); and 143 monozygotic twin families; of whom, 74 had an additional sibling and 13 with two siblings. In addition, there were 56 (non-twin) sibling pairings, 9 trios and 1 quadruplet pairing (these included cases of unpaired twins with a sibling), with a further 133 unpaired twins/sibling. Of this sample, 93% had been assessed for the short-term memory phenotype.

The sample is 98% Caucasian, predominantly Anglo-Celtic ($\sim$82%) and is typical of the Queensland population on a range of traits including intellectual ability.[40] The age range for this sample was 11 and 26 years, with a mean age of 17.5 ± 3; 47.4% of participants were male. Blood sample was obtained from twins, siblings and from 72.8% of parents for blood grouping and DNA extraction. Zygosity of same-sex twins was diagnosed using nine polymorphic DNA microsatellite markers (AmpF1STR Profiler Plus Amplification Kit, ABI, Foster City, CA, USA) and three blood groups (ABO, MNS and Rh), giving a probability of correct assignment $>99.99\%$.[41] Ethical approval for this study was received from the Human Research Ethics Committee, Queensland

Institute of Medical Research. Written informed consent was obtained from each participant and their parent/guardian (if younger than 18 years) before phenotype and blood collection.

Measures and procedure

Regular-word, irregular-word and nonword reading and spelling were assessed using the CORE,[42] a reliable 120-word extended version of the Castles and Coltheart[43] test with additional items included to increase the difficulty level for an older sample. This test was administered over the telephone by a trained researcher. From the language test battery, we focus on WAIS Digit span forward, a measure of verbal short-term memory.[44]

Test scores on each of the three reading subtests and three spelling tests were calculated as a simple sum of correct items and were Box–Cox[45] transformed to normalize their distributions. Intelligence was used as a covariate in all cases, as controlling for general cognitive ability has been shown to increase sensitivity for reading ability.[25] As scores on the verbal IQ are confounded with reading ability, performance IQ was used as a covariate, using performance scales from the Multidimensional Aptitude Battery[46] completed by 1064 subjects as close as possible to their 16th birthday (siblings were a year older on average than twins at the time of testing).

Genotyping

Three SNPs typed by Taipale *et al.*[1] (1259CG, rs61761345/1249GT and rs3743205) and one (rs11629841) by Wigg *et al.*[27] were selected for typing. An additional 14 tag SNPs were selected by the Tagger program in Haploview (http://www.broadinstitute.org/haploview/). Of these 18, 6 were excluded (including rs11629841) because they failed during the assay design or provided unreliable genotype data. The SNP 1259CG reported by Taipale *et al.*[1] had a minor allele frequency of only 0.002.

Assays were designed using the Sequenom MassARRAY Assay Design (version 3.0) software (Sequenom, San Diego, CA, USA). Forward and reverse PCR primers and a primer extension probes were purchased from Bioneer Corporation (Daejeon, Korea).[47] Genotyping was carried out in standard 384-well plates with 12.5 ng genomic DNA used per sample. We used a modified Sequenom protocol, in which half reaction volumes were used in each of the PCR, Shrimp Alkaline Phosphatase and iPLEX stages giving a total reaction volume of 5.5 μl. The iPLEX reaction products were desalted by diluting samples with 18 μl of water and 3 μl SpectroCLEAN resin (Sequenom) and then were spotted on a SpectroChip (Sequenom), processed and analyzed on a Compact MALDI-TOF Mass Spectrometer by MassARRAY Workstation software (version 3.3) (Sequenom). Allele calls for each 384-well plate were reviewed using the cluster tool in the SpectroTyper software (Sequenom) to evaluate assay quality. Genotype error checking, including Mendelian inconsistencies, and tests of Hardy–Weinberg equilibrium were performed in Pedstats[48] and Sib-pair.[49]

Association analysis

Single-nucleotide polymorphism and haplotype association analyses were carried out with QTDT[50] and Mendel[51] using a family-based association. Both programs allow monozygotic twins to be included in the analysis, although monozygotic twins' phenotypic scores are effectively averaged. In line with previous studies,[1,27] additive models were considered and were evaluated against the null hypothesis of no linkage or association. Univariate analyses of the traits included the covariates of age (and age squared), sex and performance IQ, all of which were significant at $P<0.001$. For a SNP explaining 1% of variance in our traits, under an additive model and against a background sibling correlation of 0.30, we have roughly 97% power ($\alpha=0.05$) to detect overall association with a SNP with minor allele frequency above 0.05.[52] The potential effects of multiple testing are critical in association studies, and, in addition to closely attending to both the prior expectations and the specific SNPs and effect directions in earlier studies, significance levels were controlled using matSpD to identify independent SNPs and phenotypes.[53]

Results

Descriptive

Call rates of at least 98% were achieved for all SNPs and Mendelian inconsistencies made up 0.51% of the data. Genotype screening showed that the population was in Hardy–Weinberg equilibrium at all SNPs. Allele frequencies were consistent with previous reports; a minor allele frequency of 0.002 was observed for 1259CG, consistent with Wigg *et al.*'s report of low polymorphism at this marker (see Table 1). The physical locations of the SNPs (and their intermarker linkage disequilibrium (LD)) are schematically presented in Figure 1.

Results of the family-based association tests for the individual SNPs are shown in Table 1. Population stratification was significant ($P<0.05$) for the following markers (and variables): rs61761345 (regular spelling), rs692690 (nonword reading) and rs3743205 (nonword spelling), but within-family association for these markers and variables was nonsignificant. For all other markers and variables, tests of total association were performed.

Significant association was found between rs17819126 and all three reading measures, as well as irregular word spelling, whereas both irregular and nonword reading showed marginal and significant association, respectively, with rs3743204. The digits-forward measure of short-term memory was significantly associated with the marker rs685935. For the marker rs17189126, the mean effect size was 0.21 s.d., with the major allele conferring poorer reading scores. The rs3743204 major allele was also related to worse performance (mean effect size of 0.11 s.d.), whereas the rs685935 major allele contributed to better digits-forward performance (0.22 s.d.). Correcting the

Table 1 SNP marker descriptive information, including genetic map position, gene location and minor allele frequency

SNP ID	*Position (bp)*	*Location*	*Allele*		*Reading*			*Spelling*			*STM Digits Fwd*
			Major	*Minor*[a]	*Irreg*	*Reg*	*NW*	*Irreg*	*Reg*	*NW*	
rs12324434	53501727	3′ UTR	T	C (0.39)	0.53	0.62	0.36	0.56	0.59	0.87	0.26
$1259CG_T$	53510164	Coding exon	C	G (0.002)	—	—	—	—	—	—	—
rs61761345T	53510174	Coding exon	G	T (0.09)	0.71	0.68	0.58	0.48	0.80	0.29	0.69
rs622097	53527130	Intron	C	T (0.34)	0.43	0.77	0.34	0.64	0.66	0.31	0.32
rs7181999	53547370	Intron	T	C (0.09)	0.99	0.93	0.64	0.52	0.55	0.22	0.81
rs692690	53547814	Intron	C	T (0.44)	0.65	0.76	0.42	0.90	0.46	0.96	0.32
rs685935	53558203	Intron	T	C (0.46)	0.13	0.38	0.34	0.064	0.46	0.56	**0.04**
rs8043049	53565080	Intron	C	C (0.35)	0.17	0.22	0.20	0.24	0.63	0.67	0.24
rs6493791	53568018	Intron	A	G (0.48)	0.42	0.30	0.46	0.18	0.41	0.24	0.15
rs17819126	53577202	Coding exon	C	T (0.07)	**0.0199**	0.0576	**0.0003**	**0.0086**	0.22	0.45	0.25
rs3743204	53577602	Intron (boundary)	G	T (0.21)	0.0505	0.17	**0.0089**	0.11	0.90	0.46	0.82
rs3743205T	53577822	Exon	C	T (0.07)	0.42	0.47	0.56	0.80	0.54	0.19	0.96
rs8040756	53585891	Intron	G	A (0.15)	0.63	0.88	0.95	0.92	0.47	0.16	0.27

Abbreviations: Irreg, irregular word; NW, nonword, Reg, regular word; SNP, single-nucleotide polymorphisms; STM, short-term memory; bp, base-pair position on NCBI Build 35.
SNPs with significant association are shown bold. Family-based association was performed in QTDT[50] and Mendel,[51] with covariates being age, age^2, sex and performance IQ. Additive models were evaluated against the null hypothesis of no linkage or association. SNPs subscripted 'T' are those which were significantly associated with dyslexia in Taipale *et al*.[1]
[a]Minor allele frequency in parentheses, maximum number of genotypes = 3813.

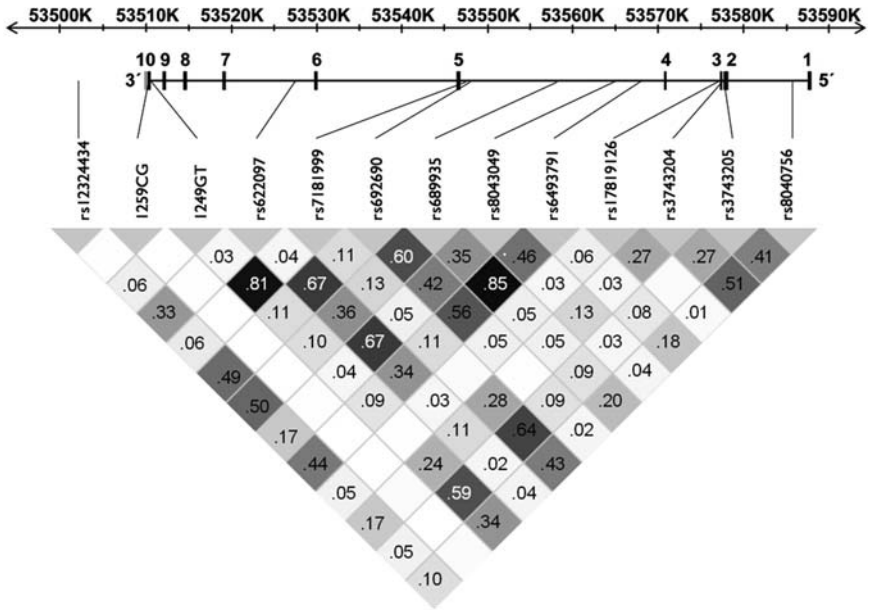

Figure 1 The location of the single-nucleotide polymorphisms (SNPs) tested across the 84-kb region of *DYX1C1*. The gene structure of *DYX1C1* is shown with exons numbered from 1 to 10 and relative exon size denoted by the width of the vertical bars. Gray bars denote untranslated regions. Inter-SNP linkage disequilibrium (shown below the gene structure) was generated using Haploview 4.0 (http://www.broad.mit.edu/mpg/haploview) and depicts the r^2 between SNPs. Cells with zero r^2 are left blank for clarity and darker shading represents stronger linkage disequilibrium.

significance level for the number of independent SNPs and phenotypes tested (10 SNPs and 2 phenotypes were identified using matSpD,[53]), rs17819126 remained significant for nonword reading at the new *P*-value cutoff of 0.0025.

The two-SNP haplotype (rs61761345 and rs3743205) shown by Taipale *et al*.[1] to influence dyslexia and confirmed by Marino *et al*.[30] for short-memory measures (but not for dyslexia[37]) was tested with Mendel. We observed similar haplotype

frequencies: GG (0.90), GT (0.03), AG (0.01) and AT (0.06), but none of the tests of association were significant (*P*-values available on request).

Discussion

Reading disorders and normal variation in learning to read have a very significant public health and social policy impact. On the basis of data translocation and association data,[1] and the role of *DYX1C1* in neuronal migration,[17,18] we examined the association of SNPs and haplotypes within and near the *DYX1C1* gene with well validated and theoretically motivated measures of reading, spelling and short-term information storage in a large (790 families) sample representative of the general population for reading and spelling ability. Among numerous positive attributes of the study were its size, utilization of normally varying and continuous trait measures assessed over multiple measures, and examination of tagging SNPs for *DYX1C1* not previously reported and derived from the HapMap[54] and tested in a population of homogenous and appropriate ethnic origin.

Support was found for association with reading ability at the exonic coding SNP rs17819126 as well as at the intronic SNP rs3743204 and, for short-term memory, at the marker rs685935. The results did not support association for the two SNPs reported as associated with dyslexia in Finnish readers.[1] These findings are consistent both with other data, suggesting that the association of markers rs3743205 and rs61761345 identified by Taipale *et al*. may be specific to the Finnish genetic background[4] and with other data suggesting that *DYX1C1* is nevertheless associated with reading disability in non-Finnish populations,[28,31] as well as with short-term memory.[28,30] Overall, these data significantly increase support for a role of *DYX1C1* in dyslexia and, perhaps separately, in short-term storage of verbal information.[30]

These data suggest a new candidate for a functional mutation in *DYX1C1*; given the known role of DYX1C1 in neuronal migration,[17,18] the results bolster the early observation of Galaburda *et al*.[55] that dyslexia may be associated with molecular layer ectopia and microgyria. Marker rs17819126, not typed in previously reported studies and identified here as being associated with reading and spelling, codes for a non-synonymous, exonic protein sequence alteration and warrants the study for its functional role in, especially, neuronal migration. In addition to its coding function in *DYX1C1*, rs17819126 is in complete LD with two SNPs in *RAB27A*, a member of the RAS oncogene family, and is in high LD with three SNPs in the nearby gene of unknown function *C15orf15*. Both *RAB27A* and *C15orf15* may, therefore, warrant further study, as does the unmeasured *DYX1C1* coding SNP rs2007494, which is in LD (r^2 of 0.84) with marker rs3743204 (1935 bp away) that was significantly associated with short-term verbal information storage and retrieval.

In addition to a role in neuronal migration, Massinen *et al*.[56] recently showed that *DYX1C1* interacts with both alpha and beta estrogen receptors, with protein levels of these receptors being reduced on overexpression of *DYX1C1*. The authors also showed *DYX1C1* to be expressed along hippocampal neurites in rats. These interactions of *DYX1C1* with estrogen occur developmentally, when they can influence neuronal architecture, and also during cognitive function, providing a second pathway for studying the effects of the protein on cognition and plasticity. Interaction with estrogen would also afford a mechanism for sex-specific effects on *DYX1C1*.

Although it is expected that genes exist which are specific for components of the reading process,[5] most reports on *DYX1C1*,[27] and other genes to date,[57] have suggested associations that are specific to the domain of reading, but not restricted to a particular subdomain of reading such as lexical storage (assessed by irregular word reading) or grapheme–phoneme conversion (assessed here by nonword reading).[58] The present results suggested some support for specificity for the effect of *DYX1C1* for nonword reading, with much stronger evidence for association with nonword reading than for irregular word reading, but markers rs17819126 and rs3743204 showed evidence for association with both subtypes of reading phenotypes, and no support for association with short-term memory. Conversely, rs3743204 was associated with short-term memory, but not with reading measures. It may be that the associations of *DYX1C1* with dyslexia and with short-term memory are mediated by distinct functional effects of mutations in this gene, perhaps by impact on tetratricopeptide repeat-domain mediated neuronal migration.[18]

Our significant association for short-term memory closely replicates that reported by Dahdouh *et al*.[28] This group found their result for haplotype rs3743205/rs3743204/rs600753. Of these three SNPS, we measured only marker rs3743204, which, in our sample, was associated with nonword reading, but not with short-term memory ($P = 0.82$). It is noteworthy that SNP rs685935, which we found was associated with short-term memory, although not typed by Dahdouh *et al*., is in LD ($r^2 = 0.74$) with rs600753 (in the Dahdouh short-term memory haplotype).

The present associations were found across sexes, whereas Dahdouh *et al*. reported that the association of *DYX1C1* with reading was significant in female trios only ($n = 66$). One explanation for this apparent divergence may include our different ascertainment process—we assessed normally varying reading, controlling for performance IQ, where the German sample was ascertained based on a clinically significant spelling-ability discrepancy from that predicted from IQ. If extreme dyslexia is less common in females and more genetic as suggested by Harlaar *et al*.,[59] then less restrictive ascertainment such as used in the present experiment would reduce differences in genetic load between the sexes. The larger sample size in the

present experiment would then explain the general finding. Alternatively, because our sample was older, differing developmental trajectories across childhood converging on similar asymptotic levels in adolescence[5,42,59,60] may also contribute to the sex-independent finding reported here. There are, then, now two reports, in two different languages, linking rs3743204 to short-term memory. Our finding suggests that this gene is not sex-limited, but may be more readily detected in younger females compared with young males because of the higher heritability of dyslexia in younger females.[29] The effect was mostly accounted for by association with short-term memory, supporting the finding of Marino *et al*.[30] that the SNPs reported by Taipale may be related more to short-term memory than to dyslexia.

Finally, as the present findings are derived from normally varying reading ability, they have additional implications for the etiology and biology of reading disability. Containing relatively few reading impaired participants and using a shorter test battery than is normally used in a clinical setting and via telephone rather than face-to-face administration, the present findings add weight to the argument[5,61] that dyslexia represents the low tail of a normal distribution of reading ability in the population, as supported by the utility of normal samples in genetic research on reading ability and dyslexia in linkage[6] and association[22,25] studies. The implication then is that the same genes influence both poor and exceptionally able reading ability. These results increase support for DYX1C1 in reading and suggest additional research to identify the specific mechanism of this association, and additional studies to identify possible pleiotropy for short-term memory. The results are compatible with the suggestion that neuronal migration is an important, unifying pathway for dyslexia, guiding future genome-wide association studies focused on pathways for neuronal migration.

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Conflict of interest

The authors declare no conflict of interest.

References

1 Taipale M, Kaminen N, Nopola-Hemmi J, Haltia T, Myllyluoma B, Lyytinen H *et al.* A candidate gene for developmental dyslexia encodes a nuclear tetratricopeptide repeat domain protein dynamically regulated in brain. *Proc Natl Acad Sci USA* 2003; **100**: 11553–11558.
2 Olson RK, Byrne B. Genetic and environmental influences on reading and language ability and disability. In: Catts HW, Kamhi AG (eds). *The Connections Between Language and Reading Disabilities*. Lawrence Erlbaum Associates: Mahwah, NJ, 2005, pp 173–200.
3 Katusic SK, Colligan RC, Barbaresi WJ, Schaid DJ, Jacobsen SJ. Incidence of reading disability in a population-based birth cohort, 1976–1982, Rochester, Minn. *Mayo Clin Proc* 2001; **76**: 1081–1092.
4 Paracchini S, Scerri T, Monaco AP. The genetic lexicon of dyslexia. *Annu Rev Genomics Hum Genet* 2007; **8**: 57–79.
5 Bates TC, Castles A, Luciano M, Wright M, Coltheart M, Martin N. Genetic and environmental bases of reading and spelling: a unified genetic dual route model. *Read Writ* 2007; **20**: 147–171.
6 Bates TC, Luciano M, Castles A, Coltheart M, Wright MJ, Martin NG. Replication of reported linkages for dyslexia and spelling and suggestive evidence for novel regions on chromosomes 4 and 17. *Eur J Hum Genet* 2007; **15**: 194–203.
7 Smith SD, Kimberling WJ, Pennington BF, Lubs HA. Specific reading disability: identification of an inherited form through linkage analysis. *Science* 1983; **219**: 1345–1347.
8 Bisgaard ML, Eiberg H, Møller N, Niebuhr E, Mohr J. Dyslexia and chromosome 15 heteromorphism: negative lod score in a Danish material. *Clin Genet* 1987; **32**: 118–119.
9 Rabin M, Wen XL, Hepburn M, Lubs HA, Feldman E, Duara R. Suggestive linkage of developmental dyslexia to chromosome 1p34-p36. *Lancet* 1993; **342**: 178.
10 Fulker DW, Cardon LR, DeFries JC, Kimberling WJ, Pennington BF, Smith SD. Multiple regression of sib-pair data on reading to detect quantitative trait loci. *Read Writ* 1991; **3**: 299–313.
11 Smith SD, Kimberling WJ, Pennington BF. Screening for multiples genes influencing dyslexia. *Read Writ* 1991; **3**: 285–298.
12 Grigorenko EL, Wood FB, Meyer MS, Hart LA, Speed WC, Shuster A *et al.* Susceptibility loci for distinct components of developmental dyslexia on chromosomes 6 and 15. *Am J Hum Genet* 1997; **60**: 27–39.
13 Schulte-Körne G, Grimm T, Nothen MM, Muller-Myhsok B, Cichon S, Vogt IR *et al.* Evidence for linkage of spelling disability to chromosome 15. *Am J Hum Genet* 1998; **63**: 279–282.
14 Morris DW, Robinson L, Turic D, Duke M, Webb V, Milham C *et al.* Family-based association mapping provides evidence for a gene for reading disability on chromosome 15q. *Hum Mol Genet* 2000; **9**: 843–848.
15 Marino C, Giorda R, Vanzin L, Nobile M, Lorusso ML, Baschirotto C *et al.* A locus on 15q15-15qter influences dyslexia: further support from a transmission/disequilibrium study in an Italian speaking population. *J Med Genet* 2004; **41**: 42–46.
16 Chapman NH, Igo RP, Thomson JB, Matsushita M, Brkanac Z, Holzman T *et al.* Linkage analyses of four regions previously implicated in dyslexia: confirmation of a locus on chromosome 15q. *Am J Med Genet B Neuropsychiatr Genet* 2004; **131B**: 67–75.
17 Threlkeld SW, McClure MM, Bai J, Wang Y, LoTurco JJ, Rosen GD *et al.* Developmental disruptions and behavioral impairments in rats following *in utero* RNAi of Dyx1c1. *Brain Res Bull* 2007; **71**: 508–514.
18 Wang Y, Paramasivam M, Thomas A, Bai J, Kaminen-Ahola N, Kere J *et al.* DYX1C1 functions in neuronal migration in developing neocortex. *Neuroscience* 2006; **143**: 515–522.
19 Rosen GD, Bai J, Wang Y, Fiondella CG, Threlkeld SW, LoTurco JJ *et al.* Disruption of neuronal migration by RNAi of Dyx1c1 results in neocortical and hippocampal malformations. *Cereb Cortex* 2007; **17**: 2562–2572.
20 Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N. Developmental dyslexia: four consecutive patients with cortical anomalies. *Ann Neurol* 1985; **18**: 222–233.
21 Cope NA, Hill G, van den Bree M, Harold D, Moskvina V, Green EK *et al.* No support for association between Dyslexia Susceptibility 1

Candidate 1 and developmental dyslexia. *Mol Psychiatry* 2005; **10**: 237–238.
22 Paracchini S, Steer CD, Buckingham LL, Morris AP, Ring S, Scerri T *et al.* Association of the KIAA0319 dyslexia susceptibility gene with reading skills in the general population. *Am J Psychiatry* 2008; **165**: 1576–1584.
23 Meng H, Hager K, Held M, Page GP, Olson RK, Pennington BF *et al.* TDT-association analysis of EKN1 and dyslexia in a Colorado twin cohort. *Hum Genet* 2005; **118**: 87–90.
24 Schumacher J, Anthoni H, Dahdouh F, Konig IR, Hillmer AM, Kluck N *et al.* Strong genetic evidence of DCDC2 as a susceptibility gene for dyslexia. *Am J Hum Genet* 2006; **78**: 52–62.
25 Luciano M, Lind PA, Duffy DL, Castles A, Wright MJ, Montgomery GW *et al.* A haplotype spanning KIAA0319 and TTRAP is associated with normal variation in reading and spelling ability. *Biol Psychiatry* 2007; **62**: 811–817.
26 Lind PA, Luciano M, Wright MJ, Montgomery GW, Martin NG, Bates TC. Dyslexia and DCDC2: normal variation in reading and spelling is associated with DCDC2 polymorphisms in an Australian population sample. *Eur J Hum Genet* 2009 (under review).
27 Wigg KG, Couto JM, Feng Y, Anderson B, Cate-Carter TD, Macciardi F *et al.* Support for EKN1 as the susceptibility locus for dyslexia on 15q21. *Mol Psychiatry* 2004; **9**: 1111–1121.
28 Dahdouh F, Anthoni H, Tapia-Paez I, Peyrard-Janvid M, Schulte-Korne G, Warnke A *et al.* Further evidence for DYX1C1 as a susceptibility factor for dyslexia. *Psychiatr Genet* 2009; **19**: 59–63.
29 Harlaar N, Spinath FM, Dale PS, Plomin R. Genetic influences on early word recognition abilities and disabilities: a study of 7-year-old twins. *J Child Psychol Psychiat* 2005; **46**: 373–384.
30 Marino C, Citterio A, Giorda R, Facoetti A, Menozzi G, Vanzin L *et al.* Association of short-term memory with a variant within DYX1C1 in developmental dyslexia. *Genes Brain Behav* 2007; **6**: 640–646.
31 Brkanac Z, Chapman NH, Matsushita MM, Chun L, Nielsen K, Cochrane E *et al.* Evaluation of candidate genes for DYX1 and DYX2 in families with dyslexia. *Am J Med Genet B Neuropsychiatr Genet* 2007; **144B**: 556–560.
32 Scerri TS, Fisher SE, Francks C, MacPhie IL, Paracchini S, Richardson AJ *et al.* Putative functional alleles of DYX1C1 are not associated with dyslexia susceptibility in a large sample of sibling pairs from the UK. *J Med Genet* 2004; **41**: 853–857.
33 Cope NA, Hill G, van den Bree M, Harold D, Moskvina V, Green EK *et al.* No support for association between Dyslexia Susceptibility 1 Candidate 1 and developmental dyslexia. *Mol Psychiatry* 2005; **10**: 237–238.
34 Bellini G, Bravaccio C, Calamoneri F, Donatella Cocuzza M, Fiorillo P, Gagliano A *et al.* No evidence for association between dyslexia and DYX1C1 functional variants in a group of children and adolescents from Southern Italy. *J Mol Neurosci* 2005; **27**: 311–314.
35 Fisher SE, Francks C. Genes, cognition and dyslexia: learning to read the genome. *Trends Cogn Sci* 2006; **10**: 250–257.
36 Morris DW, Ivanov D, Robinson L, Williams N, Stevenson J, Owen MJ *et al.* Association analysis of two candidate phospholipase genes that map to the chromosome 15q15.1-15.3 region associated with reading disability. *Am J Med Genet B Neuropsychiatr Genet* 2004; **129B**: 97–103.
37 Marino C, Giorda R, Luisa Lorusso M, Vanzin L, Salandi N, Nobile M *et al.* A family-based association study does not support DYX1C1 on 15q21.3 as a candidate gene in developmental dyslexia. *Eur J Hum Genet* 2005; **13**: 491–499.
38 McGregor B, Pfitzner J, Zhu G, Grace M, Eldridge A, Pearson J *et al.* Genetic and environmental contributions to size, color, shape, and other characteristics of melanocytic naevi in a sample of adolescent twins. *Genet Epidemiol* 1999; **16**: 40–53.
39 Wright MJ, De Geus E, Ando J, Luciano M, Posthuma D, Ono Y *et al.* Genetics of cognition: outline of a collaborative twin study. *Twin Res* 2001; **4**: 48–56.
40 Schousboe K, Willemsen G, Kyvik KO, Mortensen J, Boomsma DI, Cornes BK *et al.* Sex differences in heritability of BMI: a comparative study of results from twin studies in eight countries. *Twin Res* 2003; **6**: 409–421.
41 Nyholt DR. On the probability of dizygotic twins being concordant for two alleles at multiple polymorphic loci. *Twin Res Hum Genet* 2006; **9**: 194–197.
42 Bates TC, Castles A, Coltheart M, Gillespie N, Wright M, Martin NG. Behaviour genetic analyses of reading and spelling: a component processes approach. *Aust J Psychol* 2004; **56**: 115–126.
43 Castles A, Coltheart M. Varieties of developmental dyslexia. *Cognition* 1993; **47**: 149–180.
44 Wechsler D. *Wechsler Adult Intelligence Scale III*. Psychological Corporation: San Antonio, 1997.
45 Box GEP, Cox DR. An analysis of transformations. *J R Stat Soc Series B Stat Methodol* 1964; **26**: 211–246.
46 Jackson DN. *Multidimensional Aptitude Battery Manual*, vol. 1. Research Psychologists Press: Port Huron, MI, 1984, pp 255–264.
47 Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* 2005; **21**: 263–265.
48 Wigginton JE, Abecasis GR. PEDSTATS: descriptive statistics, graphics and quality assessment for gene mapping data. *Bioinformatics* 2005; **21**: 3445–3447.
49 Duffy DL. Sib-pair. 1.00b. http://www.qimr.edu.au/davidD/#sib-pair (accessed March 2009).
50 Abecasis GR, Cardon LR, Cookson WO. A general test of association for quantitative traits in nuclear families. *Am J Hum Genet* 2000; **66**: 279–292.
51 Lange K, Sinsheimer JS, Sobel E. Association testing with Mendel. *Genet Epidemiol* 2005; **29**: 36–50.
52 Purcell S, Cherny SS, Sham PC. Genetic Power Calculator: design of linkage and association genetic mapping studies of complex traits. *Bioinformatics* 2003; **19**: 149–150.
53 Nyholt DR. A simple correction for multiple testing for SNPs in linkage disequilibrium with each other. *Am J Hum Genet* 2004; **74**: 765–769.
54 Altshuler D, Brooks LD, Chakravarti C, Collins FS, Daly MJ, Donnelly P. A haplotype map of the human genome. *Nature* 2005; **437**: 1299–1320.
55 Galaburda AM, LoTurco J, Ramus F, Fitch RH, Rosen GD. From genes to behavior in developmental dyslexia. *Nat Neurosci* 2006; **9**: 1213–1217.
56 Massinen S, Tammimies K, Tapia-Paez I, Matsson H, Hokkanen ME, Soderberg O *et al.* Functional interaction of DYX1C1 with estrogen receptors suggests involvement of hormonal pathways in dyslexia. *Hum Mol Genet* 2009; **18**: 2802–2812.
57 Marlow AJ, Fisher SE, Francks C, MacPhie IL, Cherny S, Richardson A *et al.* Use of multivariate linkage analysis for dissection of a complex cognitive trait. *Am J Hum Genet* 2003; **72**: 561–570.
58 Coltheart M, Rastle K, Perry C, Langdon R, Ziegler J. DRC: a dual route cascaded model of visual word recognition and reading aloud. *Psychol Rev* 2001; **108**: 204–256.
59 Harlaar N, Spinath FM, Dale PS, Plomin R. Genetic influences on early word recognition abilities and disabilities: a study of 7-year-old twins. *J Child Psychol Psychiatry* 2005; **46**: 373–384.
60 Wadsworth SJ, DeFries JC. Genetic etiology of reading difficulties in boys and girls. *Twin Res Hum Genet* 2005; **8**: 594–601.
61 Shaywitz SE, Escobar MD, Shaywitz BA, Fletcher JM, Makuch R. Evidence that dyslexia may represent the lower tail of a normal distribution of reading ability. *N Engl J Med* 1992; **326**: 145–150.