ARCHIVAL REPORT

Three Dyslexia Susceptibility Genes, DYX1C1, DCDC2, and KIAA0319, Affect Temporo-Parietal White Matter Structure

Fahimeh Darki, Myriam Peyrard-Janvid, Hans Matsson, Juha Kere, and Torkel Klingberg

Background: Volume and integrity of white matter correlate with reading ability, but the underlying factors contributing to this variability are unknown.

Methods: We investigated single nucleotide polymorphisms in three genes previously associated with dyslexia and implicated in neuronal migration (*DYX1C1*, *DCDC2*, *KIAA0319*) and white matter volume in a cohort of 76 children and young adults from the general population.

Results: We found that all three genes contained polymorphisms that were significantly associated with white matter volume in the left temporo-parietal region and that white matter volume influenced reading ability.

Conclusions: The identified region contained white matter pathways connecting the middle temporal gyrus with the inferior parietal lobe. The finding links previous neuroimaging and genetic results and proposes a mechanism underlying variability in reading ability in both normal and impaired readers.

Key Words: Diffusion tensor imaging, dyslexia genes, general population, reading ability, single nucleotide polymorphism, SNP

Reading is a complex cognitive activity, requiring the recruitment of multiple brain regions. Insights into the neurobiology of reading are provided by neuroimaging studies of typical adult readers, development of reading in children, as well as by studies of developmental dyslexia, a specific reading disability exhibited in 5%–15% of the population (1,2). Anatomically, dyslexia has been associated with nested neurons, so-called ectopias, in language regions of both male and female subjects, which might relate to disturbed neuronal migration early in life (3,4). Functional neuroimaging studies have shown altered deviant activation in subjects with dyslexia, including lower activation of the left temporal, inferior parietal and occipito-temporal regions (5–7). Cortical thickness is also affected in similar regions (8).

Dyslexic individuals have also shown disturbances of white matter structure in the left temporo-parietal region (9). Interestingly, variability in white matter structure not only differentiates impaired from nonimpaired subjects but also correlates with variability in reading ability among typically developing children and adults (9–12). This shows that connectivity between language regions is crucial for reading. Secondly, these findings suggest that the same neural mechanisms could underlie both the normal variability in reading ability and dyslexia. However, the cause for this variability is not yet known. In this study, we hypothesized that polymorphisms in genes associated with dyslexia and implicated in neuronal migration in early brain development would affect variability of white matter structure in typically developing children and young adults and contribute to variability in reading ability.

A number of genes have been associated with dyslexia, and the three most consistently replicated genes are *DYX1C1*, *DCDC2*, and *KIAA0319* (13–18). Some previous studies have failed to replicate the association between *DYX1C1* and dyslexia in samples from the United Kingdom, Italy, United States, and India (19–22). However, it should be noted that the sample sizes used were relatively small, and differences exist in association test designs between original publications and replication attempts. All three genes are involved in neuronal migration, as seen in rat knock-down experiments (14,23,24). In the *DYX1C1* knock-down animal models, disturbances in neuronal migration lead to ectopias and changes in both gray and white matter structure. Recent studies have also suggested that polymorphisms in some of the *DYX1C1*, *KIAA0319*, and *DCDC2* genes are related to normal variability in reading ability (25–28) and to brain activation in language related-regions (29).

In this study, we genotyped 13 single nucleotide polymorphisms (SNPs), in or near the vicinity of three genes *DYX1C1*, *DCDC2*, and *KIAA0319* in a group of 76 randomly selected 6–25-year-old children and young adults. Volume of white matter was measured with a T1-weighted magnetic resonance sequence, and microstructure of white matter was investigated by diffusion tensor imaging (DTI). These measurements were then repeated 2 years later in 69 of the subjects. The use of a developmental sample and longitudinal design allowed us also to investigate whether any genetic effect was constant across age or whether it interacted with age. The former would suggest a very early effect on brain development only, whereas the latter would suggest an effect on the gradual maturation of white matter during childhood, such as myelination.

Methods and Materials

Participants

Seventy-six healthy Swedish-speaking children and young adults (age range 6 to 25 years, 41 male and 35 female subjects) without any evidence of neurological or psychological disorders were randomly selected from the population register in the city of Nynäshamn to participate (see [30,31] for further description of the cohort). On the basis of available parent reports, in most (89%) cases the participants and both of their parents were born in Sweden, 9% had at least one parent born outside of Sweden but within Europe, and the remaining 2% had one or both parents born outside of Europe. This study was approved by the local ethics committee of the Karolinska University Hospital. Written informed consent was obtained from each participant and the parents of those participants younger than 18 years old. On the basis of parent reports, one subject had dyslexia, and two were under investigation for dyslexia. The data from these subjects did not deviate significantly from the statistical analysis models (genetics vs. white matter and white matter vs. reading residuals, standardized residuals <2 SDs in both cases). Imaging and behavioral assessments were performed for all the participants and repeated two years later for 69 of them.

Image Acquisition and Processing

Three-dimensional structural T1-weighted imaging (magnetization-prepared rapid gradient echo sequence, repetition time =

From the Neuroscience Department (FD, TK), Karolinska Institutet, Stockholm; Department of Biosciences and Nutrition (MP-J, HM, JK), Karolinska Institutet, Huddinge; Science for Life Laboratory (JK), Karolinska Institutet, Solna, Sweden; and the Research Programs Unit (JK), Haartman Institute, University of Helsinki, and Folkhälsan Institute of Genetics, Helsinki, Finland.

Address correspondence to Torkel Klingberg, M.D., Ph.D., Department of Neuroscience, Karolinska Institutet, Retzius v. 8, Stockholm 171 76, Sweden; E-mail: torkel.klingberg@ki.se.

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2300 msec, echo time = 2.92 msec) with a 256 × 256 mm field of view, 176 sagittal slices, and 1 mm^3 voxel size was carried out with a 1.5T Avanto scanner (Siemens Medical System, Inc., Erlangen, Germany) on the participants and repeated after two years for 69 subjects. GRAPPA parallel imaging technique with an acceleration factor of two was also employed to speed up the acquisition.

White matter segmentation was performed on the structural data with a Voxel-Based Morphometry tool available via SPM5 (www.fil.ion.ucl.ac.uk/spm/software/spm5) and followed by an alignment technique performed with the Diffeomorphic Anatomical Registration with Exponentiated Lie algebra (DARTEL) toolbox in SPM. This method iteratively aligned the white matter images from both timepoint 1 and timepoint 2 to their common average template. The modulated images were then spatially smoothed with a Gaussian kernel size of 8 mm and registered to Montreal Neurological Institute space. Because the DARTEL morphing was applied to tissue segmented images, output images were the tissue probability maps in which each voxel shows the probabilty of being locally expanded or contracted in each white matter structure.

Diffusion tensor imaging was acquired with a field of view of 230 × 230 mm^2, matrix size of 128 × 128, 19 slices with 6.5 mm thickness, and b-value of 1000 sec/mm^2 in 20 gradient directions. Eddy current and head motions were corrected with affine registration to a reference volume with FSL software (www.fmrib.ox.ac.uk/fsl/). The diffusion tensors were then computed for each voxel, and the DTI and fractional anisotropy (FA) data were constructed. Tract-Based Spatial Statistics, TBSS v1.2, (fsl.fmrib.ox.ac.uk/fsl/tbss/) was applied to align all FA images to the mean FA image. In this step, the TBSS inverse transformation method was used to find the region of interest (ROI) projected on the FA data of all individuals. Deterministic fibers were obtained from 30 randomly selected subjects by starting tractography from the ROI following the principal eigenvector direction with 1 mm steps, considering thresholds of .15 for FA values and 30 for angular degree, with ExploreDTI v4.7.3. (www.exploredti.com). These 30 subjects were selected randomly from the total imaging sample, and the distribution of their genotypes was not significantly different from the whole sample ($p > .32$ assessed by χ^2 test), so they represent the whole imaging sample. The computed tracts of all individuals were then transformed to the mean FA template with the same TBSS transformation matrices already used for each subject to mean normalization.

Behavioral Assessment

The reading comprehension task for this study was administered either individually or in groups of two to 20 participants in a classroom setting. To measure reading comprehension, narrative and expository texts from the Progress in International Reading Literacy Trend Study and The International Association for the Evaluation of Educational Achievement Reading Literacy Study 1991 were employed. Seventy-seven items were used to form reading comprehension tests for four age groups from 8 to 25 years old. An item response theory analysis was used to achieve an ability score for each subject.

Because reading comprehension encompasses a range of cognitive processes, including not only language-specific aspects but also attention and working memory, we also administrated a second test of word decoding, called "word chains." This is similar to the English Woodcock Johnson Word-ID test, in which the subjects read as many words as possible during a 2-min period and get a score on the basis of the number of correctly read words (32).

Genotyping

Material for DNA extraction was collected from all subjects in form of blood from finger tips or saliva. Genotyping of 13 SNPs located in or in close vicinity to the three genes—*DYX1C1*: rs3743204, rs3743205, and rs17819126; *DCDC2*: rs793842, rs793862, rs807701, rs2328819, rs2792682, rs7751169, and rs9460974; *KIAA0319*: rs4504469, rs6935076, and rs2143340—was performed with matrix-assisted laser desorption/ionization-time of flight mass spectrometry with iPlex Gold assays according to instructions of the manufacturer as follows: polymerase chain reaction assays and associated extension reactions were designed with the MassArray assay design 3.1 software (Sequenom; www.sequenom.com). Primers were acquired from Metabion GmbH (Planegg-Martinsried, Germany). Amplification reactions were run in a total volume of 5 μL with 10 ng of genomic DNA and 1 pmol of the amplification primer, 100 nmol/L of each deoxynucleotide triphosphate, 1.625 mmol/L of magnesium chloride, and .5 U of HotStarTaq DNA polymerase (Qiagen, Crawley, West Sussex, United Kingdom). Reactions were heated at 95°C for 15 min and thereafter subjected to 45 cycles of amplification (20 sec at 94°C, 30 sec at 56°C, 60 sec at 72°C) before a final extension of 3 min at 72°C. Unincorporated deoxyribonucleotide triphosphates were dephosphorylated by addition of .3 U shrimp alkaline phosphatase. Extension reactions were carried out in a total volume of 9 μL with .625–1.25 μmol/L extension primer, and the Iplex Gold Reagents Kit Clean primer extension products were analyzed by a MassARRAY mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany). For peak identification, the SpectroT RT3.3.0/4.0 software (Sequenom) was used.

The genotyping of all SNPs studied here was originally performed in a larger sample of 335 individuals, of which 76 were randomly selected to participate in the magnetic resonance imaging. The SNPs were validated with DNA from a set of 14 trios (42 individuals) with genotype data available through the HapMap consortium. Furthermore, two independent scorers confirmed all genotypes and re-genotyping of 5% of the study samples resulted in 100% concordance. Concordance analyses with the HapMap data resulted in 100% concordance. The average genotyping success rate for all 13 SNPs reported here was 98.9%.

Statistical Analysis

All of the 13 SNPs were entered separately as a main factor in a flexible factorial design second-level SPM analysis (www.fil.ion.ucl.ac.uk/spm/software/spm5), which included both the individual images with and without repeated measures, to assess the variation of white matter volume with respect to genetic markers. This analysis was corrected for the effect of age, gender, handedness, and total white matter volume. Age × gene and gender × gene interaction effects were also added into the model. As a part of this exploratory analysis the significance level was corrected at the cluster level with nonstationary cluster extent correction (33). We corrected for multiple comparison of searching the entire white matter volume (with the threshold of $p < .05$) and, in addition, for the analysis of 13 SNPs (Bonferroni correction, with $p_{corrected} < .0038$). The 3dClustSim program of the AFNI toolkit (http://afni.nimh.nih.gov/afni) was used to determine the cluster size threshold by Monte-Carlo simulation (uncorrected significant level = .05, cluster significant level = .0038, cluster size threshold = 2285 voxels).

The significant regions were saved as binary ROIs and then entered in MarsBar SPM toolbox (http://marsbar.sourceforge.net) to compute the mean white matter volume. The mean values were then analyzed with linear mixed models in SPSS Statistics v. 20 (IBM Corporation, Somers, New York) to assess whether the white matter volume in these regions might correlate with the reading ability.

Results

After co-registering the imaging data to a common template, white matter volume was used as the dependent variable in a flexible factorial model with SPM5. This measure reflects signal intensity modulated

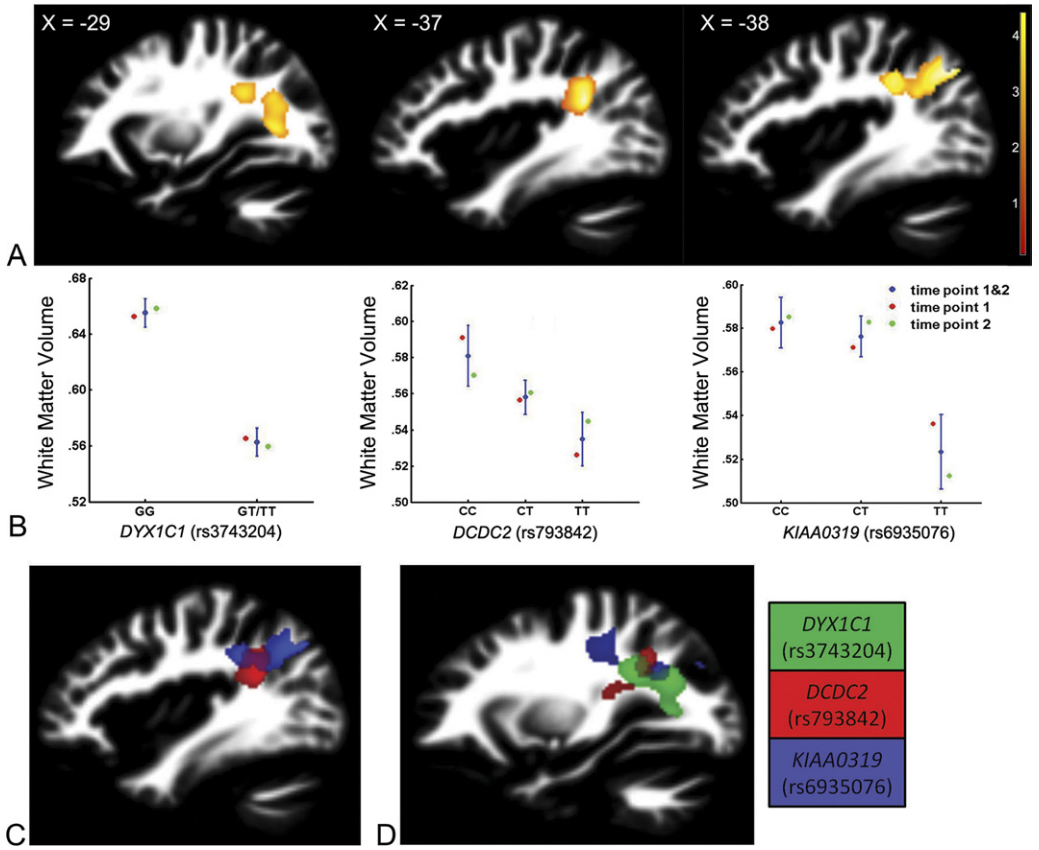

Figure 1. Main effect of three single nucleotide polymorphisms (SNPs) from the *DYX1C1*, *DCDC2*, and *KIAA0319* genes on white matter structure. **(A)** White matter clusters showing significant association between SNPs and white matter volume. All images are sagittal sections from the left tempo-parietal region. **(B)** White matter volume distribution for genotypes of each SNP (error bars: ± 1 SEM). **(C, D)** Overlap between the significant regions.

by local expansion or contraction of volume. A separate analysis was performed for each of the 13 SNPs to investigate whether any of these polymorphisms affected white matter volume. Age, gender, handedness, and total white matter volume were entered as covariates.

Genetic Associations

Three of the 13 SNPs, rs3743204 (*DYX1C1*), rs793842 (*DCDC2*), and rs6935076 (*KIAA0319*), had a significant effect on white matter volume (Bonferroni correction, with $p_{corrected} < .0038$ corrected for multiple comparison in each SPM analysis) (Figure 1A, B). Image analysis resulted in four significant clusters (Table 1). Three of the clusters, one of each associated with rs3743204, rs793842, and rs6935076, were all located in the left temporo-parietal region and partially overlapped with each other (Figure 1C, D). One additional cluster associated with rs3743204 was located in the similar location in right hemisphere (data not shown).

Table 1. Coordinates for the Effect of SNPs on White Matter

SNP	$p_{corrected}$ Cluster Level	*Z* Score	x, y, z (MNI)
rs3743204 (*DYX1C1*)	3.10×10^{-3}	3.85	−15, −54, 16
	5.43×10^{-4}	3.70	13, −35, 30
rs793842 (*DCDC2*)	1.51×10^{-3}	4.23	−37, −49, 23
rs6935076 (*KIAA0319*)	5.51×10^{-4}	4.10	−38, −69, 38

MNI, Montreal Neurological Institute; SNP, single nucleotide polymorphism.

White matter volume in these regions showed consistent association with rs3743204, rs793842, and rs6935076 at both time points of measurement, separated by 2 years (both $p < .011$) (Figure 1B). There was no significant gene × age interaction in these regions for rs793842 (*DCDC2*) or rs6935076 (*KIAA0319*), but for rs3743204 (*DYX1C1*) there was a gene × age interaction ($p = .0018$) in a region overlapping with the main effect area in the left hemisphere (Figure 2A). The interaction resulted in larger gene effect at higher ages (Figure 2B).

All analyses were corrected for the effect of white matter volume. In an additional analysis, we assessed the correlation of total white matter volume with all 3 SNPs. Rs3743204 significantly ($p = .003$) correlated with total white matter volume, after correction for age, gender, and handedness, showing the association of this SNP with white matter both locally and globally.

Tract Tracing

From DTI data we analyzed the connectivity of the white matter clusters identified by the genetic analysis. Although all significant clusters in the left hemisphere overlapped (Figure 1D), this overlap was found to be too small to generate consistent fiber tracking results from a large group of subjects. The second most consistent region was the overlap between clusters associated with *DCDC2* and *KIAA0319* (Figure 1C). This region was mainly located in the left superior longitudinal fasciculus and the corpus callosum according to the John Hopkins Probabilistic Atlas (www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html#wm). We then identified tracts that passed through this ROI. For this purpose, the ROI was registered to the diffusion weighted image of each individual. Streamline fiber

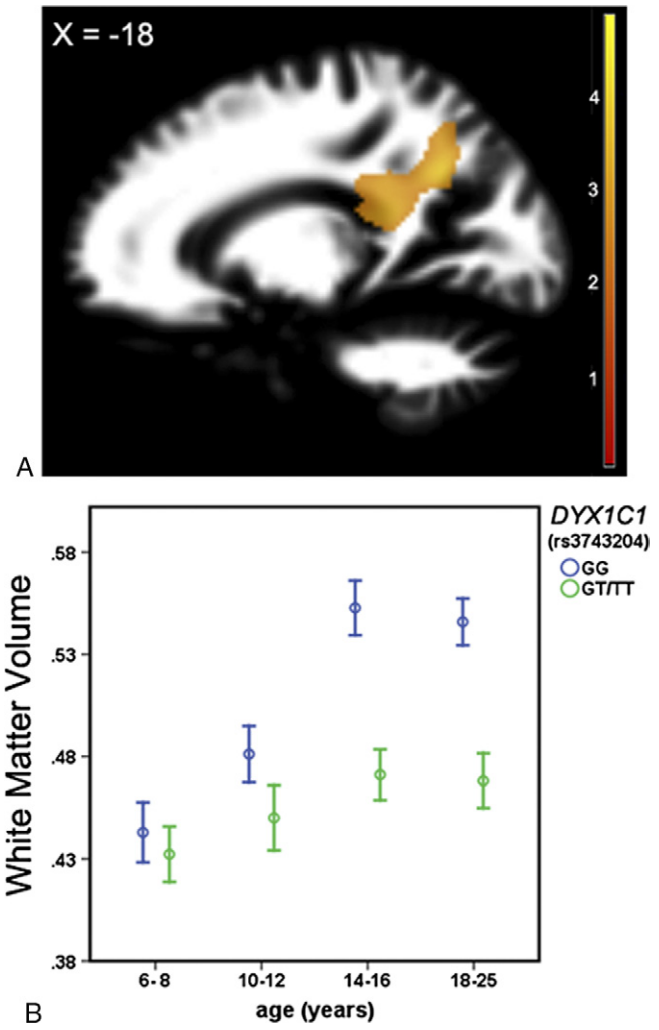

Figure 2. The *DYX1C1* (rs3743204) interaction with age. **(A)** Cluster found significant for age × rs3743204 interaction in left hemisphere. **(B)** White matter volume variations and genotypes in the different age groups (error bars: ± 1 SEM).

tracking was then performed on 30 randomly selected subjects (see Figure 3A for tracking of one individual). To have a probability map of those tractography results, all 30 tract maps were transformed back into a common space, converted into a binary image before being averaged across all individuals (Figure 3B). Finally, the probability map was overlaid on the Harvard-Oxford cortical atlas (www.cma.mgh.harvard.edu/fsl_atlas.html) to localize the cortical areas in which the tracts terminated (Figure 3C). The pathways passing through the ROI were found to be part of temporo-parietal and inter-hemispheric tracts. After "peeling off" the surface of the brain, we found that the temporo-parietal tracts connected the middle temporal gyrus to the left angular and supramarginal gyri. The endpoints of the fibers are consistent with the areas previously reported by Paulesu *et al.* (5) for middle temporal gyrus and by Richlan *et al.* (6) for inferior parietal lobule (Figure 3D). The inter-hemispheric pathways terminated mainly in the left and right superior parietal lobules and in the superior division of the lateral occipital cortex.

Behavioral Associations

The mean white matter volume in each significant cluster associated with each SNP was extracted for all subjects and then correlated with their reading scores using a mixed linear model.

First, the correlation between SNPs and white matter was confirmed, as first shown by the SPM analysis (with age, gender, handedness, and whole white matter volume as covariates). Second, white matter volume was found to be significantly correlated with reading scores (Figure 3E) in all clusters (all $p < .00009$), with greater white matter volume associated with better reading. Correlation between white matter volume, in all three clusters in left hemisphere, and reading scores survived the significant level after correcting for the effect of age, gender, and handedness ($p < .004$). In contrast, there was no significant correlation directly between these SNPs and reading scores with the same covariates.

The second reading test was "word chains" test, in which the subjects read as many words as possible during a 2-min period and received a score on the basis of the number of correctly read words (32). Again, white matter values correlated significantly with accuracy ($p < .0001$ for all tests), whereas there was no significant correlation between SNPs and accuracy. Correlation between white matter volume and accuracy remained significant after correcting for the effect of age, gender, and handedness ($p < .002$).

Discussion

Here we showed that polymorphisms in three genes previously associated with dyslexia and neuronal migration all affected white matter volume in the left temporo-parietal region of the brain. The three genetic associations pointed to the same overlapping region, with a high joint significance, and the effect remained across two different time points, 2 years apart. The results will require replication in an independent sample of individuals, because the sample size is considered small for a genetic study.

The genetic associations with white matter observed in this study are close to and partly overlapping with previously reported white matter regions associated with reading (9–12). Previous studies have been inconsistent with regard to the connectivity of reading-related white matter regions. For this study, we used tract tracing and analyzed voxel-wise consistency of location in a larger sample than in any of the previous studies in the literature. Although interindividual variability is large, we found that the most consistent connectivity was between the middle temporal gyrus/superior temporal sulcus and the supramarginal and angular gyri. These cortical areas are under-activated in subjects with dyslexia (5,6,34,35). Activity in these regions correlates with the development of reading in children (36), and they show volumetric changes in adults learning to read (37). The present study thus connects genetic findings with previous structural and functional neuroimaging studies of both normal and impaired readers.

Several previous studies have found associations between anterior–posterior connections and language function. However, there are reports of individuals with normal language function but an absence of long-ranging temporo-frontal connections (38). Our results emphasize the importance of temporo-parietal connectivity, but we cannot exclude the possibility that there might be additional frontal connectivity, not identified here due to low spatial resolution of the DTI data that the tract tracing was based on.

White matter volume could reflect the number or thickness of axons or the amount of myelination. In the present study, there was no interaction between age and the genetic polymorphisms for *DCDC2* or *KIAA0319*. This speaks against an effect on childhood brain maturation, such as myelination or increased axonal thickness, at least after 6 years of age. Instead it suggests an effect on early brain development, such as neuronal migration affecting the number of axons. For *DYX1C1*, there was both a main effect of gene and a gene × age interaction, possibly reflecting the participation of *DYX1C1* not only in early brain development but also in pathways that could affect later myelination (18).

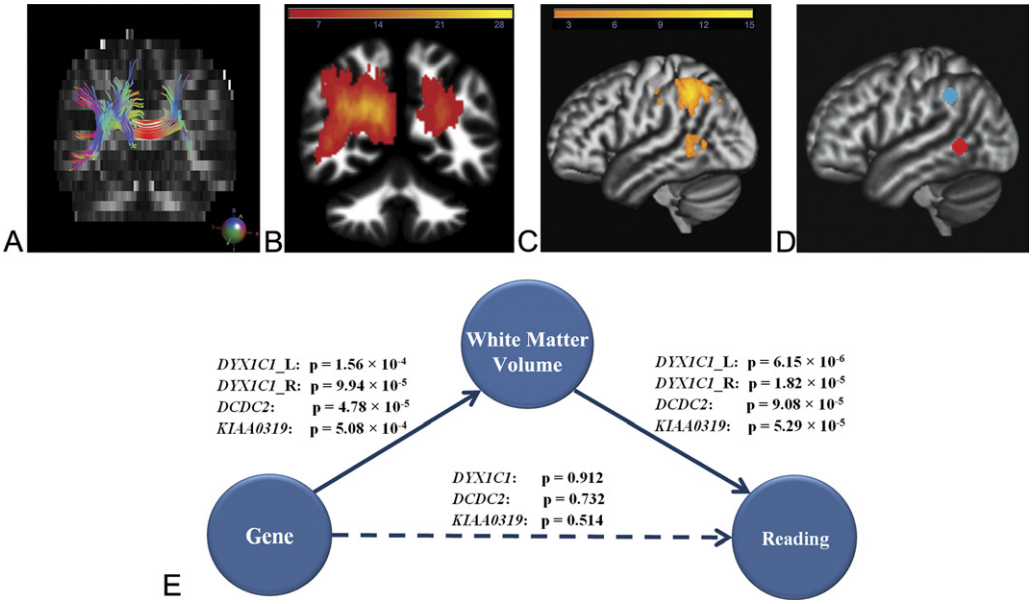

Figure 3. White matter connections and correlation to behavior. **(A)** Example of tract tracing results from one individual (red, green, and blue fibers show left–right, anterior–posterior, and inferior–superior directions, respectively). **(B)** Overlay of tract tracing from 30 individuals. The color bar shows the number of individuals with overlapping connections. **(C)** The cortical regions most consistently connected are the middle temporal gyrus/superior temporal sulcus inferiorly and supramarginal and angular gyrus superiorly. **(D)** Regions of interest drown by the radius of 5 mm at the centers of −60, −56, 0 (reported by Paulesu *et al.* [5] for middle temporal) and −38, −48, 40 (reported by Richlan *et al.* [6] for inferior parietal lobule). **(E)** Correlations between genes (SNPs), white matter volume, and reading (reading comprehension test). *DYX1C1*_L and *DYX1C1*_R denote the clusters found for rs3743204, in the left and the right hemispheres, respectively.

A very early impairment in dyslexia is suggested by analysis of event-related potentials showing that phonological deficits in subjects with hereditary risk for dyslexia can be detected as early as a few weeks after birth (39). Recent data show that the protein expressed by *DCDC2* localizes in neurons to the primary cilium and associates with proteins involved in establishing cell polarity, suggesting an effect on neuronal migration (40). Interestingly, the proteins expressed by *DYX1C1* and *DCDC2* also bind to each other (Tammimies K., Tapia-Paéz I., Kere J., personal communication, August 29, 2011). A common cellular pathway for these genes might explain the common cluster region seen at the neuroanatomical level.

It is still unclear why genes affecting neuronal migration would have such a regionally specific effect in the human brain. However, it is evident that the expression of *DCDC2* and *KIAA0319* vary widely from one brain region to another, and both are highly expressed in the temporal and parietal cortex (14). Future studies of white matter development from birth to age 6 might provide additional information about possible interactions between environment and genetic polymorphism.

The rs793842 (in *DCDC2*) SNPs has, to our knowledge, not previously been reported associated with dyslexia. However, recent reports have described associations of the SNPs rs6935076 (in the first intron of *KIAA0319*) and rs3743204 (in the first intron of *DYX1C1*) with variation in normal reading ability in a twin sample from Australia (25,41). In our study, the TT genotype of rs6935076 was associated with lower white matter volume. The combination of previous reports and new data suggest a correlation between worse reading performance and lower white matter volume. For rs3743204, association was found with both irregular and non-word reading in the Australian population cohort. In our study, the GG genotype of rs3743204 was associated with higher white matter volume, whereas the rare homozygous TT cannot be distinguished from heterozygotes.

Interestingly, two of the polymorphisms studied in this report, rs3743204 and rs3743205, are part of a haplotype of three SNPs associated specifically with female dyslexic subjects in a sample of 366 German trios (17). This might argue for an involvement of sex hormone signaling pathways in dyslexia, a hypothesis strengthened by the previously shown interaction of *DYX1C1* and estrogen receptors in primary neurons (18).

In utero knockdown of *Dyx1c1* and *Kiaa0319* expression in rat brain produce a defective neuronal migration (24,41–43). A follow-up study of adult rats after *Dyx1c1* knockdown revealed neocortical and hippocampal malformations similar to those first seen in human postmortem brains of dyslexic subjects (44). Furthermore, misplaced neurons (ectopias) with abnormal radial orientation were seen in neocortex and white matter. The reported disturbances in the rat brain model system suggest that neuronal migration provide one possible candidate pathway controlling the differences in white matter structure. Considering the association of SNPs within those three genes with variation of general reading ability (25,26,45), it is tempting to speculate that the DNA variants can produce subtle expression levels changes influencing white matter volume in the developing human brain.

In summary, this study connects previous findings from genetics and imaging studies of both normal and impaired readers. Here, we suggest a neuronal mechanism in which *DYX1C1*, *DCDC2*, and *KIAA0319*, three dyslexia susceptibility genes, affect brain connectivity between the temporal and parietal regions, which in turn affects variability in reading ability.

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