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Polymorphism of *DCDC2* Reveals Differences in Cortical Morphology of Healthy Individuals—A Preliminary Voxel Based Morphometry Study

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Abstract

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Objective—The purpose of this investigation was to determine whether there is an association between the putative reading disability (RD) susceptibility gene Doublecortin Domain Containing 2 (*DCDC2*), and gray matter (GM) distribution in the brain, in a sample of healthy control individuals.

Method—Fifty-six control subjects were genotyped for an RD-associated deletion in intron 2 of *DCDC2*. Voxel based morphometry (VBM) was used to examine structural magnetic resonance imaging (MRI) scans to assess GM differences between the two groups.

Results—Individuals heterozygous for the deletion exhibited significantly higher GM volumes in reading/language and symbol-decoding related brain regions including superior, medial and inferior temporal, fusiform, hippocampal/para-hippocampal, inferior occipito-parietal, inferior and middle frontal gyri, especially in the left hemisphere. GM values correlated with published data on regional *DCDC2* expression in a lateralized manner.

Conclusions—These data suggest a role for *DCDC2* in GM distribution in language-related brain regions in healthy individuals.

Keywords

Structural imaging; Polymorphism; VBM; Dyslexia; Language

Introduction

Reading disability (RD) is a common, cognitive, neurological disorder in which twin studies have demonstrated that genes play a significant etiologic role (Meng et al. 2005). Heritability estimates have been reported to range between 44 and 75% (DeFries et al. 1987). More recent estimates of heritability assessed through a composite-reading measure in a large sample of twins show that greater than 50% of the group deficit is attributable to genetic influences (Raskind et al. 2000). Analysis of the cognitive components of reading (phonological decoding, orthographic representation/coding and phoneme awareness) also revealed similar results (Raskind et al. 2000).

Linkage and association studies have to date identified four risk genes for dyslexia, including, Doublecortin Domain Containing 2 (*DCDC2*), *KIAA0319*, *DYX1C1* and *ROBO1* (Paracchini et al. 2007). Two candidate genes are encoded on the short arm of chromosome 6 (6p22), *DCDC2* and *KIAA0319*, which have been reported to be in tight linkage disequilibrium and share many similar characteristics (Harold et al. 2006). The 6p22 locus is one of the most well characterized and replicated quantitative trait loci in linkage studies of RD (Harold et al. 2006). *DCDC2* was the most recently identified candidate gene for RD (Meng et al. 2005; Paracchini et al. 2007; Schumacher et al. 2006). Specifically, a deletion in intron 2 was shown to be associated with RD in a family based sample of individuals from the USA (Meng et al. 2005).

Compared to other genes encoded within the 6p22 RD locus, quantitative RT-PCR on healthy post-mortem human brain, shows relatively high *DCDC2* expression in hippocampus, entorhinal cortex, hypothalamus and amygdala. In inferior and medial temporal cortex, the anatomical location of the major reading centers of the brain, *DCDC2* is the most highly expressed of these genes (Meng et al. 2005; Paracchini et al. 2007).

Variation in human language regions has been shown to be under strong genetic control; therefore, direct associations with anatomic features in the brain may be measurable. (Thompson et al. 2001). In this study, we used voxel based morphometry (VBM) data from MRI scans of healthy control subjects, to determine whether the deletion is associated with GM volume, given that previous reports suggest GM volumetric anomalies in poor readers

(Brambati et al. 2004; Casanova et al. 2005; Kronbichler et al. 2007; Silani et al. 2005; Vinckenbosch et al. 2005).

Materials and methods

Fifty-six right-handed healthy volunteer individuals underwent a physical examination and were screened using psychiatric and health questionnaires. Subjects were excluded if they reported a history of cardiovascular, neurological or psychiatric disorders (including learning disabilities), head trauma (loss of consciousness >30 min), central nervous system (CNS) disease, or drug or alcohol abuse or dependence. Subjects were free from medications known to affect the CNS. Forty three subjects (age range (years): 20–85 Mean/SD (years): 41.69/18.18 Male/Female: 19/24) were homozygous for no deletion and were described as genotype 1/1. Thirteen subjects (age range (years): 19–82, Mean/SD (years): 38.23/21.12, Male/Female: 9/4) were heterozygous for the deletion and described as genotype 1/2. Individuals homozygous for the deletion (genotype 2/2) were infrequent and were omitted from the study. Groups were age ($t(df)$: 0.58(54), $p=0.57$) and sex matched (chi square=1.603, $p=0.26$). Further, groups were also found to be age matched ($p=0.86$) using a non-parametric Kolmogorov–Smirnov (KS) statistic. The institutional review board of Hartford Hospital approved the project and participants provided written informed consent.

Scans were performed on a 3T Siemens Allegra scanner (Siemens, Erlangen Germany) at the Olin Neuropsychiatry Research Center. High resolution 3D MPRAGE images were acquired on all subjects (FOV=176×256 mm², matrix size=176×256, slice thickness 1 mm, yielding a resolution of 1×1×1 mm³, echo time (TE) of 2.74 ms, repetition time (TR) of 2,500 ms, inversion time (TI) of 900 ms, flip angle of 8°).

The intron 2 deletion of *DCDC2* was genotyped by allele-specific PCR as previously described (Meng et al. 2005). Images were analyzed with the optimized VBM approach (Good et al. 2001) using SPM2 software (<http://www.fil.ion.ucl.ac.uk/spm/software/spm2/>) running on MATLAB version 6.5. We created customized gray matter, white matter and CSF templates using data from all 56 subjects. Customized templates were created to better match sample contrast and demographics. As part of the optimized VBM protocol, all images were run through an iterative segmentation and normalization protocol as detailed in Good et al. 2001. The optimized approach aims to reduce misclassification of gray matter and thus improves the utility of segmented images towards a voxel-wise comparison approach. Jacobian modulation was applied during VBM to preserve the absolute volume of GM. Images were then smoothed with a 12 mm FWHM isotropic Gaussian kernel before performing a voxel-wise group comparison.

A two-sample t -test within the general linear model framework in SPM2 was used to investigate group differences in GM volume. Statistical parametric maps were created seeking volumetric differences for both genotype 1/1 > genotype 1/2 and genotype 1/2 > genotype 1/1. No voxels survived the correction for multiple comparison (FDR at $p<0.05$). All results are therefore reported at the $p<0.01$ ($t=2.4$; $df=54$) uncorrected level with a cluster threshold of $k=20$ voxels corrected for non-stationarity (Hayasaka et al. 2004). Corresponding peak coordinates for each significant region is reported in Montreal Neurological Institute (MNI) space. Related effect sizes were computed using the VBM2 toolbox (<http://dbm.neuro.uni-jena.de/vbm/vbm2-for-spm2/>).

A Spearman rank correlation analysis was performed between published regional *DCDC2* expression levels in the normal, post-mortem human brain (Meng et al. 2005) and the suprathreshold GM volumes from this study (See Fig. 1). *DCDC2* expression levels were ranked relative to thalamus, which was set to a value of 1. Derived suprathreshold volumes

were clustered together based on Brodmann areas to match the published regions. The correlation was performed for multiple brain regions including inferior (BA 21, 20, 38), medial and superior (BA 22) temporal cortex, frontal (BA 44, 45) and prefrontal (BA 9, 10, 11, 46) cortex and posterior and superior parietal (BA 7) cortex. Masks were created for the above regions using the WFU pickatlas utility (http://www.fmri.wfubmc.edu/cms/software#WFU_PickAtlas). Further, custom Matlab scripts were used to calculate the extent of suprathreshold voxel volume within each of the above listed region of interest. Table 1 depicts the GM suprathreshold volume measure and *DCDC2* expression values that were used as part of the Spearman rank correlation analysis.

Masks corresponding to the above brain regions were also used to perform a small volume correction (SVC) on the main effect results to investigate regions surviving a FDR correction for multiple comparisons within the volume of interest (Salgado-Pineda et al. 2003).

To determine laterality differences, we computed laterality indices (LI) for the above mentioned language cortices using a laterality index toolbox, provided as an extension to SPM2 (Wilke and Lidzba 2007). Data clustering and variance weighting was performed to consider the effects of smoothing and residual data variance in computing the LI. LIs were computed based on un-thresholded *t*-map values to reduce thresholding bias (Holland et al. 2001).

Results

Genotype frequencies were consistent with Hardy–Weinberg equilibrium expectations ($p < .025$). Further, the frequency of the deletion was consistent with previous reports (Meng et al. 2005). Volumetric differences in GM were observed in multiple frontal and temporal regions (Fig. 2). Higher GM volume was observed in subjects with genotype 1/2 in regions including superior, medial and inferior temporal gyri, fusiform gyrus, hippocampus, uncus and parahippocampal, inferior occipito-parietal, inferior and middle frontal gyri (Fig. 2; Table 2). For several regions this was more marked in the left hemisphere.

Correlation analysis revealed a positive correlation between total suprathreshold volume (right and left combined) and expression levels of *DCDC2* ($r = 0.6$; $p = 0.28$). Analyzing the left and right hemispheres separately (see Table 1) also yielded positive correlations. However, the correlation was markedly stronger and significant in the left hemisphere ($r = 0.9$; $p = 0.03$) and was much weaker in the right hemisphere ($r = 0.3$; $p = 0.62$).

Left and right inferior temporal cortices demonstrated significantly increased GM volume in the genotype 1/2 group (FDR corrected; $p = 0.05$) when a SVC was performed. Also, regions including right superior parietal ($p < 0.15$) and left superior temporal cortex ($p < 0.15$) demonstrated a trend towards significance. Further, based on the laterality indices computed, superior temporal (LI: 0.04), inferior temporal cortices (0.10) and posterior/superior parietal cortices (LI: 0.13) were found to be left-lateralized and frontal (LI: -0.20) and prefrontal (LI: -0.10) were found to be right-lateralized for GM differences.

Discussion

This pilot study is the first to investigate the relationship between *DCDC2* and brain structure and indeed the first study to undertake this analysis for any RD susceptibility genes, although abnormalities in neuronal migration have recently been investigated with respect to *DCDC2* in embryonic rat brains (Meng et al. 2005). However, given the preliminary nature of the current study, it might be crucial to replicate and extend our results in the future involving both behavior and imaging.

While *DCDC2* is associated with RD, it is also likely that genes affecting RD will be responsible for normal variation in reading ability, thus differences in *DCDC2* effects will be observed in control individuals as studied here. Given this hypothesis and that disruption of *DCDC2* regulatory regions may affect *DCDC2* activity and consequently brain structure, we used VBM to determine whether there was an association between a deletion in *DCDC2* and GM volume in the brain.

Individuals carrying the 1/2 genotype (deletion present) had increased GM volume in brain regions compared to the group carrying the 1/1 genotype (no deletion). These included cortical regions of the superior, middle and inferior temporal gyrus, inferior, middle and superior frontal gyrus, inferior parietal lobule, fusiform gyri, extrastriate visual cortices (inferior/middle occipital gyrus), lingual gyrus and supramarginal gyrus. Differences in non-cortical regions included the hippocampus/parahippocampus, amygdala, globus pallidus and putamen. These brain regions correlate with areas identified previously as being involved in reading and/or symbol decoding either structurally or functionally (Kronbichler et al. 2007; Brambati et al. 2006; Cao et al. 2006; Casanova et al. 2005; Silani et al. 2005; Vinckenbosch et al. 2005; Aylward et al. 2003; Eckert et al. 2003; Ruff et al. 2003; Brown et al. 2001; Eliez et al. 2000; Rumsey et al. 1999).

Compared to structural imaging studies before 2005 (Brambati et al. 2004; Eckert et al. 2003; Brown et al. 2001; Eliez et al. 2000), several recent studies, using more optimized and contemporary imaging techniques, have reported mixed patterns of increased and decreased gray matter volumes in dyslexia. More specifically, these studies show increases in GM volume in several cortical areas pertaining to language including: posterior, medial and inferior temporal gyri, precentral and postcentral gyri, superior and medial frontal gyri and precuneus (Kronbichler et al. 2007; Silani et al. 2005; Vinckenbosch et al. 2005). These new data suggest that gray matter changes observed in dyslexia are not merely associated with decreases in gray matter alone and have a more complex genetic etiology.

Consistent with expectations based on known laterality differences in cortical language representation, correlation analyses between GM volume and *DCDC2* expression yielded both significant and higher results in the left hemisphere.

This study provides the first evidence that a deletion in *DCDC2* correlates with GM volume and suggests that it may exert its effects across the whole reading ability spectrum. In addition, brain regions implicated in this study concur with previous VBM reading studies and structural and functional neuroimaging methods. The higher and significant correlation between *DCDC2* gene expression levels and GM volume in the left hemisphere, suggest that *DCDC2* is acting in language-related brain systems given the laterality hypothesis of language. In the context of other VBM studies of reading and RD, where better reading is associated with increased GM volume, the deletion may have a protective effect, being associated with increased GM volume. However, we did not assess reading ability in our subjects, which awaits further study in a replication sample.

Further studies with a larger sample size are required to increase detection power. Also, it might be very important to conduct studies including RD individuals and individuals homozygous for the deletion to further investigate the effects of *DCDC2* on brain anatomy.

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Fig. 1.
RT-PCR results for *DCDC2* expression from Meng et al. (2005), in five areas of anonymous donor human brain regions (normalized to thalamus = 1)

Fig. 2. Volumetric differences (genotype1/2>genotype1/1) between groups, represented as color intensity with yellow depicting the largest difference between groups, and surface rendered on a 3D brain. Results displayed are at the $p<0.01$ uncorrected level

Table 1

Table shows the level of *DCDC2* expression in each anatomical region from published results (scaled to thalamus = 1) along with corresponding regional suprathreshold voxels in the left hemisphere, right hemisphere and combined hemispheres used towards the spearman correlation analysis

Language regions (Brodmann areas)	<i>DCDC2</i> expression levels	Suprathreshold voxel volume within region of interest Left (CC)	Suprathreshold voxel volume within region of interest Right (CC)	Suprathreshold voxel volume within region of interest Total (CC)
Parietal cortex superior (BA 7)	0.87	0.03	1.73	1.76
Prefrontal cortex (BA 9,10,11,46)	1.3	0.44	1.72	2.16
Temporal cortex inferior (BA 21, 20, 38)	1.7	12.72	10.77	23.49
Temporal cortex superior (BA 22)	1.17	0.01	0	0.01
Frontal cortex (BA 44,45)	1.11	0	1.18	1.18

Table 2

Columns depict anatomical label, MNI coordinate for peak activation voxel in each brain region, *t*-scores and effect size from random effects analysis

Regions	Left vol (CC)	MNI coordinates (x,y,z)	Max <i>t</i> value	Effect size (d)	Right vol (CC)	MNI coordinates (x,y,z)	Max <i>t</i> value	Effect size (d)
Inferior temporal gyrus	5.8	-50.5, -3.3, -41.9	3.04	0.82	7.7	46.4, -13.6, -41.3	3.07	0.83
Superior temporal gyrus	5.8	-43.4, 22.2, -36.8	3.32	0.9	2.1	50.5, 16.1, -38.4	2.72	0.74
Uncus	5.3	-21.2, 2.8, -41.5	2.97	0.81	2	37.3, -10.6, -39.9	3.17	0.86
Middle temporal gyrus	3.6	-37.3, -6.9, -30.2	2.93	0.79	4.5	50.5, 13.0, -39.7	3.24	0.88
Postcentral gyrus	2.7	-68.6, -17.8, 28.4	2.5	0.64	0.2	62.6, -30.9, 44.0	2.6	0.7
Fusiform gyrus	2.6	-38.3, -12.2, -29.3	3.05	0.83	2.3	45.4, -37.4, -16.4	3.53	0.96
Lentiform nucleus	2.5	-29.2, -19.7, 2.2	2.91	0.8	0.6	32.3, -20.6, 0	2.56	0.7
Caudate	2.1	-18.1, -11.4, 23.3	2.65	0.73	NS	NS	NS	NS
Parahippocampal gyrus	1.9	-34.3, -16.4, -25.9	2.96	0.8	0.6	41.4, -36.6, -12.8	2.9	0.78
Inferior occipital gyrus	1.6	-34.3, -80.2, -5.8	2.96	0.8	0.6	29.2, -92.5, -7.7	2.64	0.72
Inferior frontal gyrus	1.2	-47.4, 25.0, -6.8	2.77	0.75	5.6	41.4, 25.3, 8.9	3.32	0.9
Sub-gyral	1.1	-38.3, -13.3, -25.8	3.12	0.85	0.3	45.4, -42.7, -14.3	2.83	0.77
Inferior parietal lobule	1	-67.6, -26.2, 31.2	2.58	0.7	2.9	31.3, -55.6, 41.6	3.16	0.86
Middle frontal gyrus	1	-45.4, 56.1, -9.8	2.43	0.67	1.8	34.3, 34.4, -9.9	3	0.82
Supramarginal gyrus	0.8	-63.6, -55.2, 32.9	2.58	0.7	<0.1	62.6, -46.1, 37.8	2.42	0.66
Middle occipital gyrus	0.7	-31.3, -81.2, -5.8	2.96	0.81	0.6	30.3, -94.7, -5.4	2.65	0.72
Insula	0.7	-40.4, -28.9, 0.6	2.81	0.76	NS	NS	NS	NS
Lingual gyrus	0.7	-33.3, -75.9, -9.1	2.68	0.73	0.3	17.1, -96.2, -17.4	2.56	0.7
Precuneus	0.3	-11.1, -71.9, 36.4	2.43	0.67	0.4	30.3, -75.8, 53.6	2.8	0.76
Superior frontal gyrus	0.2	-22.2, 70.8, 8.0	2.69	0.74	0.1	16.1, 6.7, 75.4	2.5	0.68
Superior parietal lobule	1.3	27.2, -58.7, 42.6	2.42	0.66	1.8	27.2, -55.6, 41.6	3.37	0.91
Angular gyrus	NS	NS	NS	NS	0.3	30.3, -58.5, 38.2	2.98	0.81
Cuneus	NS	NS	NS	NS	0.2	27.2, -94.6, -6.6	2.62	0.71

Regions show significant increases in gray matter volume for subjects with genotype 1/2 compared to genotype 1/1.