Polymorphic deletion in DCDC2 affects Brain Morphology - A Voxel Based Morphometric Study

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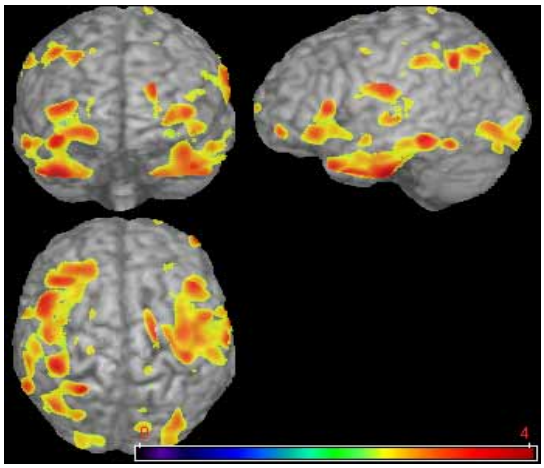
Introduction: The field of "Imaging Genetics" has evolved rapidly over the past few years. Using both structural and functional brain imaging data as intermediate phenotypes, this methodology serves as a non-invasive surrogate to probe and identify possible roles of genes or the relationship of allelic function in behavioral and cognitive outcomes. Recent findings propose doublecortin domain containing 2 (DCDC2) as a candidate gene for Reading Disability (RD). The primary aim of the current work was to examine Voxel Based Morphometric (VBM) structural gray matter differences in healthy controls, linked with a large polymorphic deletion (dbSTS BV677278) on the 6p22 chromosome within the DCDC2 gene.

Materials and Methods: A total of 56 healthy subjects were included in the study. All subjects were screened using extensive psychiatric and medical health questionnaires. 43 subjects (age range: 20-85; Mean/SD: 41.69/18.8; M:F ratio: 19:24) had homozygous alleles (11) and were categorized as genotype 1. Thirteen subjects (age range: 19-82, Mean/SD: 38.23/21.12, M:F ratio: 9:4) had heterozygous alleles (12) and were grouped as genotype 2. The third group of homozygous alleles (22) had a significantly less occurrence (3 subjs.) and was thus omitted from our study. Both the groups were age (t(df): 0.58(54), p = 0.5647) and gender matched (chi square = 1.603, p = 0.2055). All imaging was performed on a 3T Siemens Allegra. High resolution 3D MPRAGE images were acquired on all subjects with the following parameters FOV - 176x256, matrix size - 176 x 256, slice thickness -1mm, yielding an in- plane resolution of 1x1x1 mm^3, TE - 2.74 ms, TR - 2500 ms, TI - 900 ms, FA - 8^o. The optimized VBM approach was used to preprocess all images, yielding modulated gray matter images for all subjects. A 2 sample t-test was then used to assess gray matter volumetric differences between the two groups. All analyses were performed using SPM2 (http://www.fil.ion.ucl.ac.uk) running on MATLAB 6.5. We further performed a correlation analysis with previously reported results (Meng et. al. PNAS 2005) to both examine agreement and to validate our imaging results. Only language regions were selected (a subset of regions listed in fig 4 of the above reference) and ranked for corresponding DCDC2 expression levels. The language-specific regions chosen were: superior and posterior parietal cortex, prefrontal and frontal cortex, inferior, medial and superior temporal cortex. All regions in our study were transformed from MNI to Talairach space using Matthew Brett's transformation utilities. Regions were then clustered together based on Brodmann areas to match the above specified cortices chosen from existing literature. Five of these 7 regions exhibited significant gray matter differences in our study. A Spearman ranked correlation was performed between the ranked levels of DCDC2 in these regions and the suprathreshold volumetric differences observed in our study.



Language Regions (Brodmann areas)	DCDC2 expression levels	Suprathreshold volume R (CC)	Suprathreshold volume L (CC)	Total suprathreshold volume (CC)
Parietal cortex sup. (BA 7)	0.87	1.8	1.3	3.1
Prefrontal cortex (BA 9,10,11,46)	1.3	1.8	2	3.8
Temporal cortex inferior (BA 21, 20, 38)	1.7	12.5	10.5	23
Temporal cortex sup. (BA 22)	1.17	2.1	6.5	8.6
Frontal cortex (BA 44,45)	1.11	5.6	1.2	6.8

Fig 1 (Left): Volumetric differences (g2>g1) between groups, surface rendered on a 3D brain. Results displayed are at the p = 0.01 uncorrected level.

Table 1 (Above): Suprathreshold volumes observed in language regions along with manually ranked DCDC2 expression levels (in arbitrary units, normalized to thalamus = 1)

Results and Discussion: Volumetric differences in gray matter were observed in multiple frontal and temporal regions between the two groups (see table 1). Subjects with genotype 1 (homozygous alleles) exhibited significantly less gray matter volumes compared to the subjects with heterozygous alleles (genotype 2). Fig 1 displays a surface projected rendering of the morphological differences observed. Volumetric differences observed in regions that subserve language are shown in Table 1. The Spearman ranked order correlation described above yielded scores of r = 0.46 and r = 0.80 on the right and left hemispheres of the brain respectively. The correlation performed on the total suprathreshold volume (R and L combined) with the expression levels of DCDC2 yielded a positive correlation score of r = 0.70 thus complementing our imaging results. Consistent with our hypothesis, significant gray matter differences were observed in language-related areas in this healthy population. It is interesting to note that the observed correlation was higher on the left hemisphere of the brain, consistent with the laterality differences in normal cognition and language. Our initial results seem to be of interest and to have the potential to provide a quantitative imaging tool to assess the role of DCDC2 polymorphic variants in language disorders.