

BRAIN AND FUNCTIONAL ABNORMALITIES AS RESULTS OF GENETIC MUTATION WITH THE DCC (DELETED IN COLON CANCER) GENE DELETION

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Introduction

Mirror movements (MM) are synkinesias occurring in the opposite side during the intentional use of a limb. MM is occasionally present in healthy children, but persistence beyond age 10 is considered abnormal [1, 2]. The gene mutation found to cause mirror movements is called DCC (Deleted in Colorectal Carcinoma). Heterozygous mutations in *DCC* were recently identified as the cause of congenital MM in two pedigrees with multiple affected family members [3]. However, the information on neuronal substrates as the result of the genetic alterations is important but limited. Here, magnetic resonance imaging (MRI) as well as blood oxygenation level dependent (BOLD) functional MRI (fMRI) were applied to investigate the brain and functional changes associated with DCC that causes MM.

Materials and Methods

Subjects: Two affected family members (11 weeks old and 35 years old) with congenital MM were evaluated in a systematic questionnaire that queried perinatal history, development, presence of learning disabilities, and other medical history. Information regarding the onset, distribution, suppressibility, and functional and social impact of MM was obtained. Genetic analysis, genome-wide chromosomal microarray analysis using a custom designed 44K oligonucleotide array and identified a 655 kb interstitial deletion of chromosome 18q21.2 that includes the 3' end (exons 20-29) of the *DCC* gene (chr18:49229956-49884580; hg18 genome assembly). Fluorescence *in situ* hybridization (FISH) was used to confirm the findings and to test additional family members were performed.

MRI Data Collection: MRI data were recorded from the subjects on a 3T MRI scanner (Siemens Tim/Trio) using a standard head coil and a routine clinical brain MRI protocol. Adult subject with MM when using the right hand also underwent fMRI for mapping motor cortices involved in MM. The subject was asked to perform sequential finger tapping using either the left or right hand at a frequency of ~1 Hz following a block design paradigm with a time course of 70 points (3 ON and 4 OFF blocks). Image acquisition parameters include: TR/TE=3000/35 ms, Field of View (FOV) = 240 mm, matrix = 64 x 64, 25 slices and slice thickness = 5 mm without gap. Diffusion tensor images (DTI) were recorded in the axial direction with 60 slices and 2 mm thickness with no gap. Directional sensitized diffusion-weighted single-shot spin-echo EPI sequence with 20 gradient directions was used with the following imaging parameters: TR=9800 ms; TE=74 ms, b values of 0 or 1000 s/mm². DTI was collected with a matrix of 128 x 128 and then reconstructed to a matrix size of 256 x 256.

Image Process and Data Analysis: The first-level single subject analysis was performed for analyzing fMRI time course data from each subject using SPM2 software package (Wellcome Department of Cognitive Neurology, London, UK). Motion corrections were done by realigning the functional images to the 3rd volume in each run. The displacement parameters in the x, y and z directions were recorded and used to assess gross head motion. The maximum net displacement was calculated as the norm of the vector determined by the maximum absolute displacement in each direction. Spatial smoothing on the realigned images using a 6 mm full-width-half-maximum (FWHM) Gaussian kernel was performed. The general linear model (GLM) [4] implemented in SPM2. Brain activation maps were calculated based on the blocked design. An estimate of the standard canonical hemodynamic response function (HRF) was based as the basis function, and only task conditions were explicitly modeled. We also presented the data using Lateralization Index (LI) in left and right finger tapping to quantify. $LI = Vol(L) - Vol(R) / Vol(L) + Vol(R)$.

Results and Discussion

On physical evaluation, the 11-week-old female referred to genetics and was generally non-dysmorphic, but was noted to have a marked frontal hair upsweep, suggestive of abnormal brain development. FISH analysis revealed that the girl's father has the same deletion with a history of congenital MM not associated with other neurologic abnormalities. **Figure 1** showed the array results.

Anatomic MRI findings from adult subject revealed a thin corpus callosum, especially in the genu, the presence of colpocephaly, and mild atrophy in the superior portion of the cerebellum [Figure 2]. In addition, there was an abnormal hypointensity in the globus pallidus and a fifth ventricle on T2 FLAIR imaging [Figure 3]. fMRI exam with a sequential finger tapping task showed strong bilateral activations in motor cortex of hemisphere when performing the right-handed finger tap in which MM was also observed. However, motor activation was lateralized when performing left handed task [Figure 4]. LI values of the subject are 0.14 for the right handed and 0.69 for the left handed performances, respectively comparing to LI=0.68 for both right and left handed movement observed in normal controls.

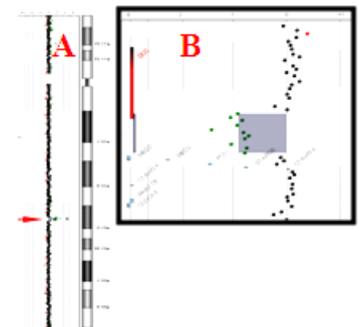


Fig 1: Chromosomal microarray analysis. (A) Array results for chromosome 18. The Y-axis displays the genomic position of the probes and the X-axis displays the log₂ ratios of the patient

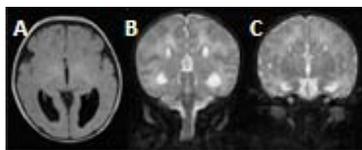


Fig 2: Brain MRI of the daughter. (A) Colpocephaly is seen in transverse sections. (B) Coronal sections reveal absence of the corpus callosum and (C) a "steer-horn" configuration of the lateral ventricles.

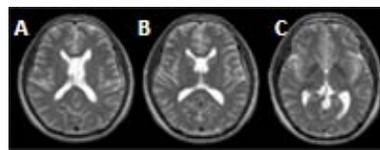


Fig 3: Brain MRI of the father. (A) There is a fourth ventricle. (B) The genu of corpus callosum appears to be thinner than normal. (C) Hypointensity in the globus pallidus was observed.

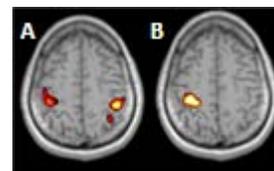
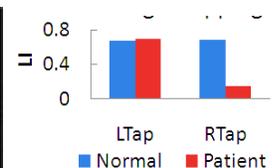


Fig 4: fMRI maps obtained from the right handed finger tapping (A) from the left hand finger tapping (B). Plot: LI values of the subject with MM and DCC mutation comparing to normal controls.



Conclusions

Our findings confirm that heterozygous deletions of the *DCC* gene, encoding a netrin-1 receptor that mediates axonal midline guidance in the developing brain, results in MM. The most likely mechanism of MM in the patient's father is abnormal activation of the contralateral primary motor cortex due to dysfunctional inhibitory transcallosal projections. This important observation provides new understanding on involuntary mirror movements and genetic mutation that may cause the brain structural abnormalities, especially of the corpus callosum.

References:

[1] Cincotta M, Ziemann U. *Clin Neurophysiol* 2008;119. [2] Rasmussen P. *Dev Med Child Neurol* 1993;35. [3] M. Srouf *et al. Science* 2010;328. [4] Della-Maggiore, V., *et al. Neuroimage*, 2002;17.