

# White matter biomarker from DTI for children with Hereditary Spastic Paraplegia (HSP)

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## Introduction

DT-MRI is sensitive to subtle white matter structural changes which play essential roles in motor dysfunction of children with Hereditary Spastic Paraplegia (HSP). HSP is a clinically and genetically heterogeneous neurodegenerative disorder characterized by progressive spastic paraparesis of the lower limbs [1,2]. Diagnosis is based on age and nature of onset, progression of symptoms, a three generation family history, clinical features, and, in some instances, genetically by mode of inheritance, chromosomal locus, or causative gene. The Gross Motor Function Classification System (GMFCS) [3] can be used to quantify "severity" of this disease related to motor outcome. Till now few studies have been conducted to survey the entire white matter to find the most sensitive white matter region which can be used for early diagnosis. Our goal is to find an effective white matter biomarker of HSP for early diagnosis. The white matter region most sensitive to the severity of motor impairment is the white matter biomarker we are seeking to identify. In this ongoing study, we have acquired high resolution DTI data from 13 HSP children and 11 age matched controls. Voxelwise analysis was performed with TBSS [4] to find the location of disrupted voxels. All subject data were registered to the template used to generate JHU digital white matter atlas [5] so that the white matter skeletons from TBSS can be parcellated into tracts for anatomical guidance. Statistically significantly FA decreases at corpus callosum (CC), several components of projection tracts, superior longitudinal fasciculus, external capsule and thalamus, were found. Further correlation of FA of these tracts and clinical GMFCS scores were conducted to find the tracts whose FA values are sensitive to severity of the motor impairment. And we found FA values of projection tract, CC and superior longitudinal fasciculus (SLF) are significantly correlated to GMFCS scores and may serve as potential white matter biomarkers.

## Methods

**Subjects and data acquisition:** Although HSP is a rare disorder, Texas Scottish Rite Hospital for Children (TSRHC) has approximately 100 pediatric patients with this diagnosis. Both 13 HSP children (age:  $8.9 \pm 2.1$ ) and 11 age matched controls (age:  $8 \pm 1.4$ ) were recruited from TSRHC. A 3T Philips Achieva MR system was used. High resolution DTI data were acquired using a single-shot EPI with SENSE. DWI parameters were: FOV=224/224/143mm, in plane imaging matrix =  $112 \times 112$ , axial slice thickness = 2.2 mm, 30 independent diffusion-weighted directions with b-value =  $1000 \text{ sec/mm}^2$ , TE=97ms, TR=7.6s. To increase signal noise ratio (SNR), two repetitions was performed. **Atlas-based quantification to locate significant clusters:** FA data of all subjects were first nonlinearly registered to the so-called "EVE" template, which is FA data of an individual subject serving as the template to set up ICBM-DTI-81 atlas [5]. This step ensures that all our FA data is well registered to the ICBM-DTI-81 atlas. Tract-based spatial statistics (TBSS) [4] of FSL was used to locate the clusters of skeleton voxels with significantly lower FA values in the template atlas space. Only clusters with voxel number greater than 10 were kept to reduce the noise effects. Multiple comparison correction was conducted with a small volume of 1000 skeleton voxels surrounding the significant clusters to control the family-wise type-I error. **Correlation of FA at disrupted clusters to GMFCS scores within HSP patients:** The significant clusters with similar functions and identified from the previous step were grouped together, indicated by the same color in Table 1. FA values of all these grouped clusters of each HSP patient were averaged and Pearson correlation was conducted with GMFCS scores as one factor and averaged FA values of cluster groups as a dependent variable.

## Results

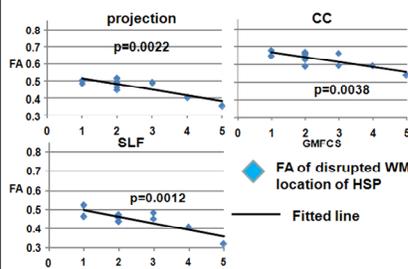
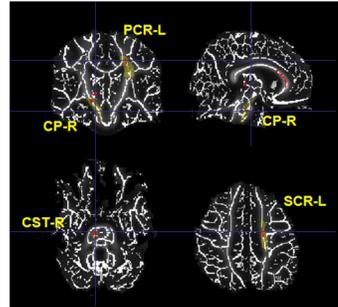
**Disrupted tracts:** The disrupted tracts including one or multiple clusters with statistically significantly lower FA values, the averaged FA values at these clusters and their statistics (FDR corrected) are listed in Table 1. Different colors indicate different functions of the tracts. Multiple components of projection tracts which are directly related to motor function are shown in Table 1. As an example, the detailed anatomical locations of disrupted clusters in projection tracts are also displayed in Fig. 1. Besides projection tracts, all

components of callosal tracts, both sides of SLF, thalamus and external capsule are also affected by HSP and included in Table 1. **Correlation of FA to GMFCS scores:** Shown in Fig. 2, Projection, callosal tracts and superior longitudinal fasciculus are significantly correlated to GMFCS scores. However, no statistical significance was found for correlation between FA of external capsule or thalamus to GMFCS.

**Table 1: Out of 50 major tracts labeled in ICBM-DTI-81 atlas, four projection tracts, all components of CC tracts, thalamus, left EC, left and right SLF have one or more clusters with significantly lower FA in HSP children.** Abbreviations of white matter tracts are as follows. BCC: Body of corpus callosum; CP: Cerebral peduncle; CST: Corticospinal tract; EC: External capsule; GCC: Genu of corpus callosum; PCR: Posterior corona radiate; SCC: Splenium of corpus callosum; SCR: Superior corona radiate; SLF: Superior longitudinal fasciculus.

## Conclusion and discussion

To the best of our knowledge, our study reveals the distribution and correlation of structural changes of white matter tracts to motor function severity of HSP children for the first time after complete survey of whole brain white matter. Disruption among all white matter tracts for HSP patients is inhomogeneous. Moreover, disruption within an affected white matter tract is also inhomogeneous and a specific region of the tract is more severely disrupted by HSP than other regions of the same tract. In addition, there is a direct relationship between the



GMFCS scores of the HSP patients. The correlation statistic and fitted linear line are also shown.

**References:** [1] Depienne, C et al (2007) Current Opinion in Neurology 20: 674. [2] Warnecke, T et al (2007) Neurology 69: 368. [3] Palisano, RJ et al (2000) Physical Therapy 80: 974. [4] Smith, SM et al (2006) NeuroImage 31:1487. [5] Mori, S et al (2008) NeuroImage 40: 572. **Acknowledgement:** This study is sponsored by NIH RR014982 and NIH EB009545.