Reciprocal alterations of white matter microstructure in carriers of deletions versus duplications at the 16p11.2 chromosomal locus are associated with cognitive and behavioral impairment

Yi-Shin Chang[1], Julia P Owen[1], Tony Thieu[1], Nicholas Pojman[1], Polina Bukshpun[1], Mari Wakahiro[1], Elysa Marco[1], Jeffrey Berman[2], John E Spiro[3], Wendy Chung[4], Randy Buckner[5], Timothy Roberts[2], Srikantan Nagarajan[1], Elliott Sherr[1], and Pratik Mukherjee[1]

[1]*University of California in San Francisco, San Francisco, California, United States,* [2]*Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States,* [3]*Simons Foundation, New York, New York, United States,* [4]*Columbia University, New York, New York, United States,* [5]*Harvard University, Boston, Massachusetts, United States*

Introduction: Copy number variants (CNVs) at the 16p11.2 chromosomal locus are associated with several neuropsychiatric disorders, including autism, schizophrenia, and bipolar disorder. Individuals with 16p11.2 deletions may have high body mass index (BMI) and large head size, while people with the reciprocal duplications often demonstrate low BMI and small head size, suggesting a gene dosage dependence. Using diffusion magnetic resonance imaging (MRI), we recently reported widespread alterations of white matter (WM) microstructure in human children with 16p11.2 deletions, compared to typically developing children [1]. In this study, we characterize and compare white matter alterations in pediatric and adult human carriers of the 16p11.2 duplication and 16p11.2 deletion, and relate these alterations to cognitive and behavioral function, as part of the Simons VIP project [2].

Methods: This study includes data from 30 pediatric deletion carriers (ages 8-16, 15M, 15 female), 13 pediatric duplication carriers (ages 7-16, 12 male, 3 female), 7 adult deletion carriers (ages 20-48, 4 male, 3 female), 23 adult duplication carriers (ages 20-63, 13 male, 10 female), and age-, gender-, and handedness-matched control participants for each cohort. Nonverbal IQ (NVIQ), verbal IQ (VIQ), and social responsiveness scale (SRS) scores were obtained for all cohorts. High resolution 3T structural MRI and whole-brain diffusion-weighted MRI using 30 directions at b=1000 s/mm^2 were acquired for all subjects. Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) maps were constructed for every subject, and mapped onto a common white matter (WM) skeleton for each cohort. Global (whole-brain) and regional FA, MD, RD and AD values were calculated from the skeletonized WM of each subject. Voxel-wise group differences of each DTI parameter were assessed for each of the four CNV carrier cohorts and their matched controls. Global and regional group differences were also assessed for the children and adults using analysis of variance (ANOVA). Finally, correlations of NVIQ, VIQ, and SRS were performed with the absolute value of z-scored DTI values, measured as standard deviations away from the control mean, in global and regional white matter.

Results: The TBSS results reveal extensive increases of FA and AD throughout the white matter in the pediatric deletion carriers relative to their controls, while the pediatric duplication carriers show extensive decreases of FA and elevations of MD and RD throughout the white matter. The adult duplication carriers similarly exhibit decreased FA and increased RD relative to their controls, but with additional extensive decreases of AD. While the adult deletion carriers are underrepresented with only seven subjects, and do not show significant voxel-wise group differences, they do exhibit significant elevations of AD in the association and limbic tracts from the ANOVA group analysis.

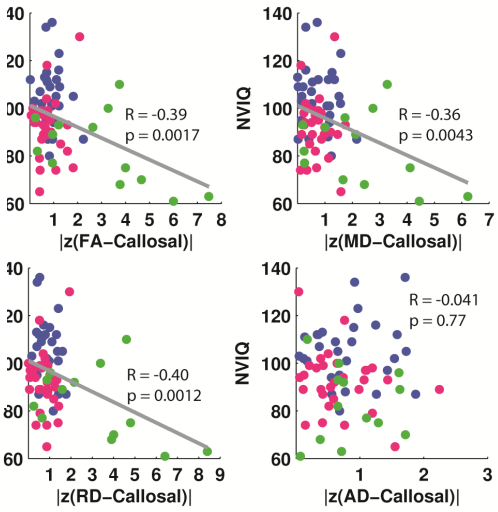

Figure 2. Cognitive correlations of NVIQ versus |z(FA)|, |z(MD)|, |z(RD)|, and |z(AD)| in callosal tracts for children. Data are from controls (blue), deletion (red) and duplication (green) carriers.

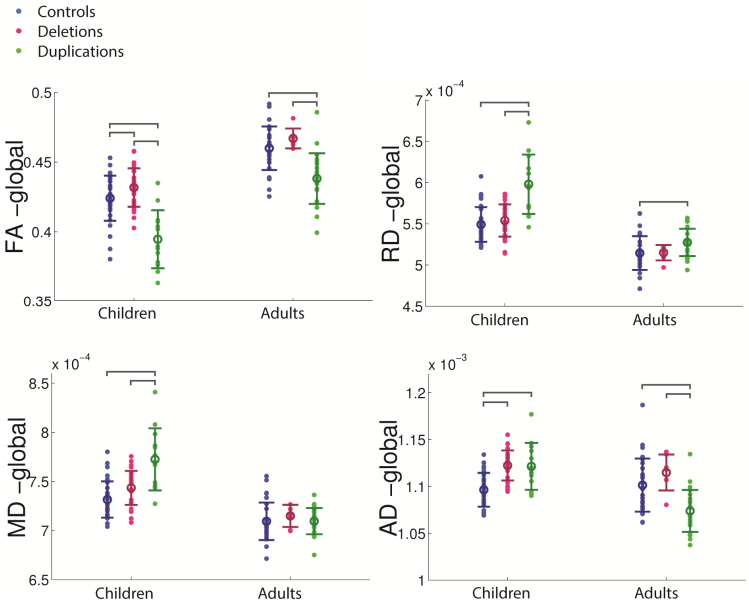

Figure 1. Group difference ANOVA results of whole-brain white matter DTI values for pediatric and adult carrier-control cohorts, with regression of NVIQ, site, and age. Significant pairwise comparisons are indicated by brackets (p<0.05, FDR corrected).

Significant correlations between NVIQ and the absolute value of z-scored DTI metrics in the callosal, association, and projection tracts were found in children. The adults showed significant correlations of NVIQ and SRS with the absolute value of z-scored DTI metrics in the callosal and limbic tracts.

Conclusions: We have demonstrated widespread and opposing white matter alterations in carriers of the 16p11.2 deletion versus the reciprocal duplication. Carriers of this deletion and duplication show reciprocal effects in FA, the most commonly used biomarker for white matter integrity, which fall in line with the theory of dosage-dependence of genes at the 16p11.2 locus. We have further shown associations of cognitive and behavioral impairment with deviation in either direction from normative microstructural white matter values. These opposing effects on white matter microstructure may elucidate the often conflicting results of DTI studies of neuropsychiatric disorders that are associated with this CNV, such as autism and schizophrenia. Our significant findings with modest sample sizes support the view that specific genetic variations may be more strongly associated with changes in brain structure, including macrostructure [3] and microstructure, than are shared neuropsychiatric diagnosis.

References:

[1] Owen JP et al, J Neurosci 2014; [2] The Simons VIP Consortium, Neuron; [3] Qureshi A et al., J Neurosci 2014