Introduction: Rare genetic copy number variations contribute to neurodevelopmental disorders including autism. Deletion and duplication of the BP4-BP5 segment of chromosome 16 at location p11.2 has been associated with developmental disorders such as dysfunctions in language, mild to moderate intellectual disability, and autism spectrum disorders (ASD). We are motivated to examine the auditory and language systems in these children given prior structural and functional findings in subjects with ASD. Diffusion MR is sensitive to white matter architecture and has been used to detect white matter abnormalities in language and auditory pathways associated with ASD [1]. Magnetoencephalography has shown delayed latency of the auditory evoked field in ASD [2]. The auditory radiation carries sensory input to the auditory cortex, Heschl’s gyrus is a hub for auditory and language circuits, and the arcuate fasciculus is integral to language function. This study uses diffusion tensor imaging (DTI) and high angular resolution diffusion imaging (HARDI) to quantify alterations in these auditory and language pathways in children with 16p11.2 deletions and duplications.

Methods: This work included children imaged at two institutions participating in a multisite study. Imaging was performed on a 3T Siemens Trio scanner with a 32 channel head coil. Diffusion tensor imaging (DTI) was acquired from 37 controls (mean age 12.6 yrs, range 8.5-17), 29 deletion carriers (mean age 11.2 yrs, range 8-16), and 14 duplication carriers (mean age 10.2 years, range 7-14.5). DTI included 30 gradient directions at \( b=1000s/mm^2 \) and 2mm isotropic resolution. HARDI was acquired in a subset of 37 controls, 27 deletion carriers, and 10 duplication carriers. HARDI included 64 gradient directions at \( b=3000s/mm^2 \) and 2mm isotropic resolution. Non-verbal IQ was measured by certified child psychologists. DTI from the \( b=1000s/mm^2 \) acquisition was measured in the auditory radiation, white matter of Heschl’s gyrus, and the arcuate fasciculus. The arcuate fasciculus was defined with deterministic DTI tractography [3], Heschl’s gyrus was defined with the FreeSurfer white matter parcellation [4], and the auditory radiation was defined with probabilistic HARDI tractography [5]. Left and right hemisphere structures were averaged. Linear regression covarying for age and non-verbal IQ was used to compare controls and subjects with copy number variations. Multiple comparisons between the 3 groups were performed with a Tukey test.

Results: Analysis of variance revealed a significant effect of genetic copy number variation on FA, MD, and radial diffusivity in each of the regions measured (\( p<0.05 \)). Figure 2 shows genetic copy number variations are associated with increased MD and radial diffusivity and with decreased FA in Heschl’s gyrus. In the auditory radiation, duplication and deletion subjects each exhibited higher MD (\( p<0.05 \)). In the arcuate fasciculus, duplication subjects exhibited higher MD, higher radial diffusivity, and lower FA than controls (\( p<0.05 \)).

Discussion: The alterations to white matter microstructure are similar to those observed in developmental disorders, particularly ASD. Mean and radial diffusivities were consistently higher in the copy number variation groups indicating alterations of white matter microstructure which may impair function. Quantitative assessment of functionally specific regions with diffusion MR will allow us to correlate white matter microstructure with findings from electrophysiological auditory and language measures (MEG) and neuropsychiatric testing. This and other studies provide insight into the connection between the genetic etiology of autism and brain phenotype.

References: