

Different genetic mutations are associated with different abnormal patterns of language white matter pathways in young children with global developmental delay

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Targeted audience: Clinical researchers using diffusion tensor imaging to study pediatric neurological disorders.

Purpose: Global developmental delay (GD) refers to an etiologically heterogeneous set of neurodevelopmental disorders mediated in part by multiple genetic mutations¹. The present study investigates whether a "maximum a posteriori probability (MAP)" classifier, a diffusion weighted imaging (DWI) tractography method, can be used to detect unique patterns in axonal language pathways, which may be correlated to different types of genetic mutations observed in children with GD. **Methods:** 6 right handed children with GD (age: 46.8±15.1 months, 5 boys) having mutations in MID1, CDK4, SFRP1, EN2, RXRG-GLRB, or MECP2, and 5 right handed children with typical development (TD, age:

48.5±20.5, 4 boys) underwent a 3T diffusion weighted MRI with eight channel head coil at TR = 12,500ms, TE = 88.7ms, FOV = 24cm, 128x128 acquisition matrix (nominal resolution = 1.89mm), contiguous 3mm thickness in order to cover entire axial slices of whole brain using 55 isotropic gradient directions with b= 1000s/mm², one b=0 acquisition, and number of excitations (NEX)=1. For each subject, whole brain tractography using independent component analysis with ball and stick model (ICA+BSM)² was sorted using a DWI-MAP classifier³ in order to identify five language pathways, C₁: Broca's area to Wernicke's area", "C₂: Broca's area to premotor area", "C₃: premotor area to Wernicke's area", "C₄: premotor to inferior parietal area", and "C₅: Wernicke's area to inferior parietal area in left hemisphere. The fiber volume of individual pathways was assessed by summing the voxels belonging to the streamlines of each pathway. Finally, to

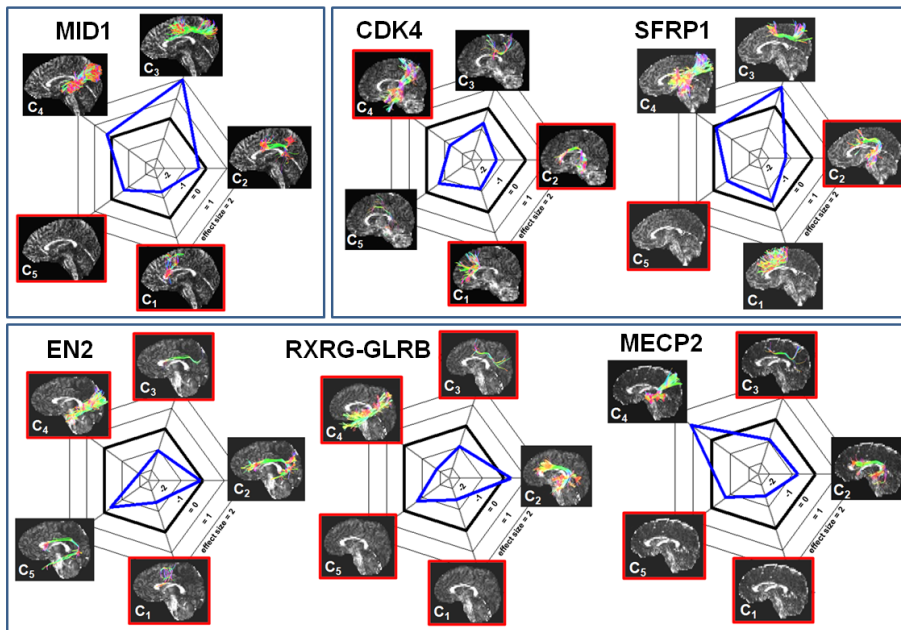


Figure 1. Radar plots showing abnormally developed volumic change in five language pathways of GD children having different mutations. For each GD child, the effect sizes were assessed in five different pathways (blue line). Each image enclosed by red box shows individual pathway of DWI-MAP classifier having apparently reduced fiber volume compared with TD group (i.e., effect size < -1).

quantify the degree of volume change in individual pathways of each child with GD, an effect size was evaluated using the following equation: effect size = $(v - m_{TD}) / \text{std}_{TD}$ where v is the fiber volume of the child with GD. m_{TD} and std_{TD} represent average and standard deviation of fiber volume in TD group, respectively). **Results:** Compared with the TD group, the children with GD had unique patterns of volume changes in different pathways (i.e., significantly *reduced* fiber volumes in different pathways, **Fig. 1**). Interestingly, there were three separate clusters showing similar patterns. For instance, the child with a MID1 mutation showed reduced volume only in the premotor area. Mutations in CDK4 and SFRP1 had reduced volume in both Wernicke's area and the premotor area. Mutations in EN2, RXRG-GLRB, and MECP2 had the reduction in most language areas, which may be related to severe language impairment. **Discussion and Conclusion:** The present preliminary study suggests that the pattern of language network abnormality may differ with specific mutations in children with GD. These different alterations may aid in understanding the biology of language impairment in GD and may assist in the development of effective imaging biomarkers of GD. More studies and replication in larger numbers of children are required to further establish detailed and specific genotype-phenotype relationship of GD. **References:** 1. Gopal SP, Tiwari VN, Veenstra AL, et al. Sensitive diffusion tensor imaging quantification method to identify language pathway abnormalities in children with developmental delay. *J Pediatr*, 2012;160:147-15. 2. Jeong JW, Asano E, Yeh FC, et al. Independent component analysis tractography combined with a ball-stick model to isolate intra-voxel crossing fibers of the corticospinal tracts in clinical diffusion MRI. *Magn Reson Med*. 2013;70:441-53. 3. Jeong JW, Asano E, Juhász C, et al. Localization of specific language pathways using diffusion weighted imaging tractography for presurgical planning of children with intractable epilepsy. *Epilepsia*, 2014 in press.