

## Effect of mutation location on Duchenne brain morphology

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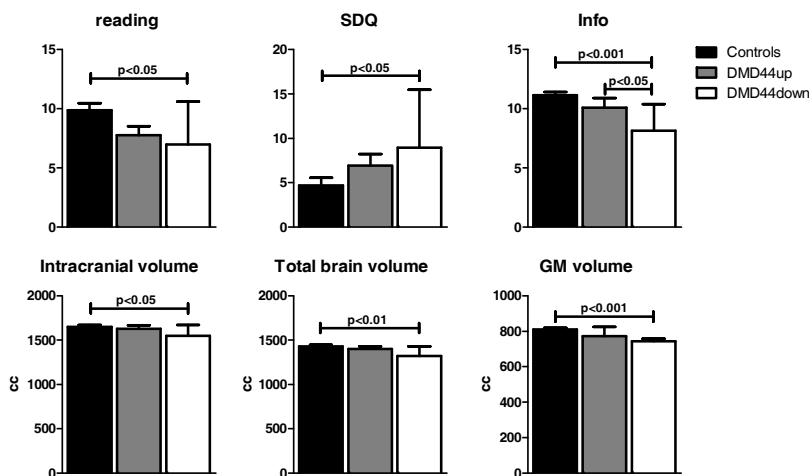
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**Target audience:** Medical professionals involved in Duchenne Muscular Dystrophy (DMD)

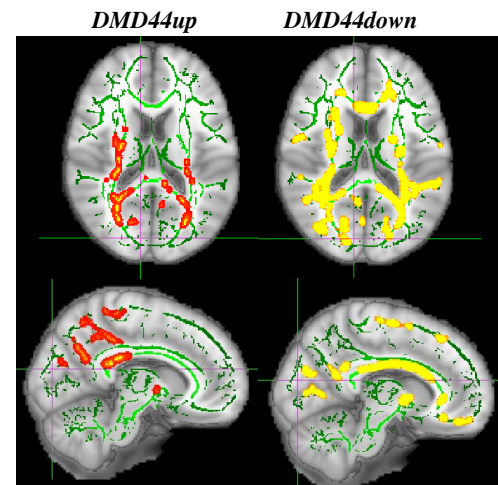
**Purpose:** To study brain morphology in DMD patients with different mutations in the *DMD* gene. In DMD, mutations in the *DMD* gene lead to absence of the full length dystrophin protein which results in progressive muscle weakness. Dystrophin is normally also expressed in brain, both the full length protein as well as shorter isoforms, but little is known about their function except that mutations downstream of exon 44 in the gene are known to be implicated in the cognitive deficits associated with DMD<sup>1</sup>.

**Methods:** 13 DMD patients with a mutation upstream of exon 44 (DMD44up) and 16 DMD patients with a mutation downstream of exon 44 (DMD44down) were compared to 22 healthy age and sex matched controls (ages 8-18 years). In the DMD44down group no production of the shorter isoform Dp140 is expected. A neuropsychological (NP) test battery was administered and condensed into three composite scores; reading, information processing (Info) and strengths-and-difficulties-behavior (SDQ) problem scores. 3D T1weighted (TE/TR 4.6 ms/9.8 ms, resolution 1x1x1 mm, 4:55min) and DTI (TE/TR 56 ms/9440 ms, resolution 2x2x2 mm, 32 directions, 6:40min) images were obtained at 3T (Philips Achieva) using an 8 channel head coil. FSL<sup>2</sup> version 5 was used for all quantitative analyses. ExploreDTI<sup>3</sup> was used for DTI motion/distortion correction. Intracranial volume (ICV), total brain volume (TBV), and volumes for grey matter (GM), white matter and cerebrospinal fluid were determined and compared between the three groups using ANOVA and post-hoc testing. Fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD) of the whole brain were measured and compared between the three groups using tract-based spatial statistics (TBSS)<sup>4</sup>.

**Results:** Group DMD44down performed significantly worse than controls in all three NP composite scores (Fig.1). ICV, TBV and GM volumes were also significantly smaller in DMD44down (Fig.1). MD (Fig.2) and RD differences between patients and controls were more profound and diffuse in DMD44down, though differences were also seen between DMD44up and controls. FA was lower in the occipital lobe in both patient groups compared to controls (data not shown).



**Fig1.** Top row: composite score results for reading (left), SDQ (middle) and Info (right). Bottom row: Intracranial (left), total brain (middle) and GM volumes (right) in cc.



**Fig 2.** Mean diffusivity TBSS results showing higher mean diffusivity compared to controls in red ( $p < 0.05$ ) and yellow ( $p < 0.001$ ).

**Discussion:** Patients with a mutation downstream of exon 44 show more profound changes in brain morphology than patients with a mutation upstream of exon 44. We found lower scores in reading and information processing, and higher SDQ problem scores in the DMD44down group. Our results are consistent with previous neuropsychological testing which showed that the more dystrophin isoforms were affected, as is the case in the DMD44down group, the lower the IQ score<sup>1</sup>. The DMD44down patients were also most affected in terms of whole brain volume and white matter integrity. Regions with increased MD and RD show increased tissue water content in the WM microstructure. Regions with decreased FA indicate either reduced fiber density or increased membrane permeability. Dystrophin isoforms are normally present throughout the brain<sup>5</sup> and the expression of Dp140 is predominantly active during fetal development and associated with penetrating cerebromicrovasculature<sup>8</sup>. The effect of the absence of Dp140 on morphological characteristics in DMD may therefore prove vital for understanding the etiology of the learning and behavioral problems known to be associated with this disease.

**Conclusion:** Quantitative analysis of brain MRI in Duchenne muscular dystrophy shows morphological differences that correlate with mutations downstream of exon 44. This study can aid in determining the underlying mechanism of cognitive or behavioral dysfunction in DMD.

**References:** [1] Taylor et al 2010, PLoS One 20:5(1) [2] M. Jenkinson et al. 2012, NeuroImage, 62:782-90 [3] A. Leemans et al. 2009, proc ISMRM 17 3537 [4] S.M. Smith et al 2006, NeuroImage, 31:1487-1505 [5] H.G.W. Lidov et al 1996 Brain Pathology 6:63-77 [6] G.E. Morris et al 1995 Biochem. and Biophys. Res. Comm. 215(1):361-367