Longitudinal dystrophin gene expression from the fetal to adult human brain correlates with genes linked to autism spectrum disorders and intellectual disability

Ahmed Mahfouz[1,2] & Nathalie Doorenweerd[3,4,6] (equal contribution), Maaike van Putten[5], Rajaram Kaliyaperumal[5], Peter A.C. 't Hoen[5], Jan J.G.M. Verschuuren[4], Erik H. Niks[4], Marcel J.T. Reinders[2], Hermien E. Kan[3,5], Boudewijn P.F. Lelieveldt[1]

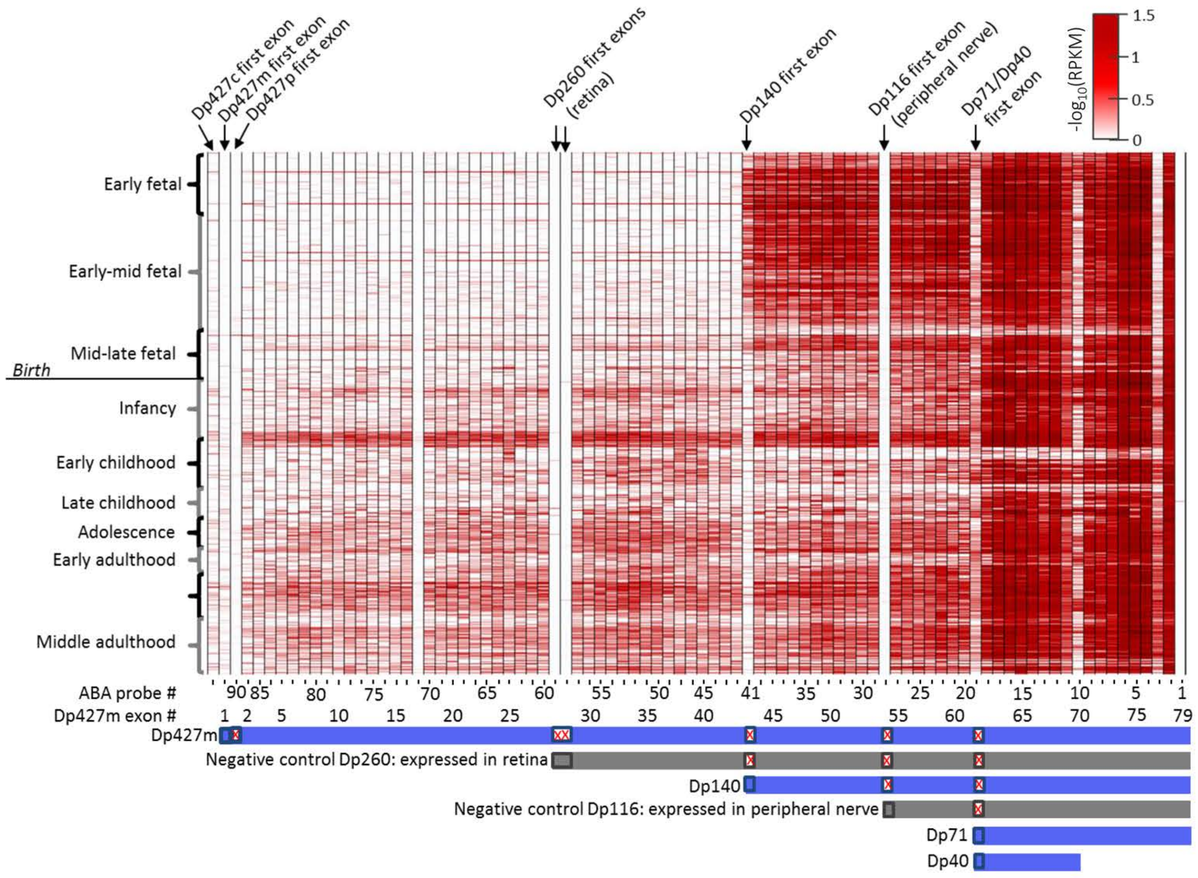
[1]Division of Image Processing, Department of Radiology, LUMC; [2]Delft Bioinformatics Lab, TU Delft; [3]C.J. Gorter Centre for High Field MRI, Department of Radiology, LUMC; [4]Department of Neurology, LUMC; [5]Department of Human Genetics, LUMC; [6]Leiden Institute for Brain and Cognition, Leiden University

Summary

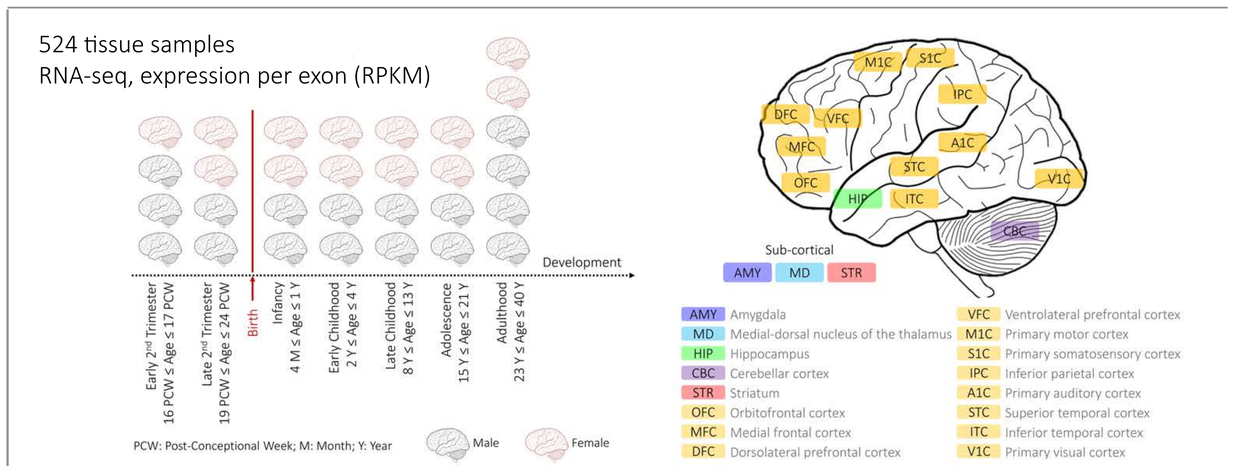
In addition to skeletal muscle pathology, Duchenne muscular dystrophy (DMD) is characterized by cognitive and behavioural problems as well as altered brain morphology. These are more substantial in patients with a DMD gene mutation affecting the expression of various shorter dystrophin isoforms in the brain. In this study, we aim to provide detailed understanding of the localization and function of the different DMD isoforms throughout brain development.

Using the developing human brain transcriptome data from the *BrainSpan*[1] *Atlas*, we analyzed the expression of the unique first exons of the diffirent DMD isoforms (Dp427(p,c,m), Dp260, Dp140, Dp116 and the shared first exon of Dp71 and Dp40) across the brain and throughout human development. In addition, we used the *Allen Human Brain Atlas*[2] to analyze the expression of the DMD gene at a higher resolution across different brain structures. Finally, we assessed the list of genes co-expressed with the different DMD isoforms across development for enrichment in genes implicated in autism spectrum disorders (ASD) and intellectual disability (ID).

DMD Isoforms Across Development

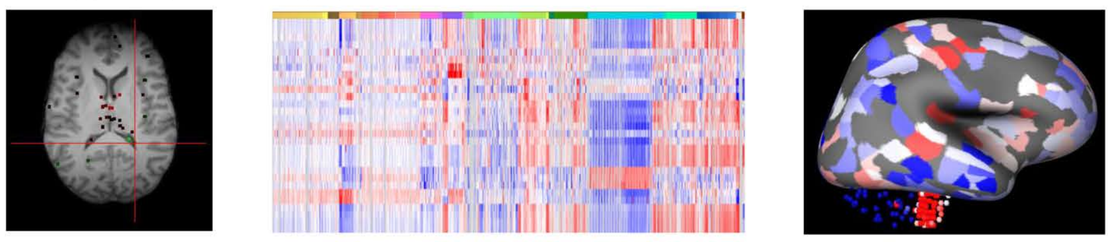


BrainSpan Atlas

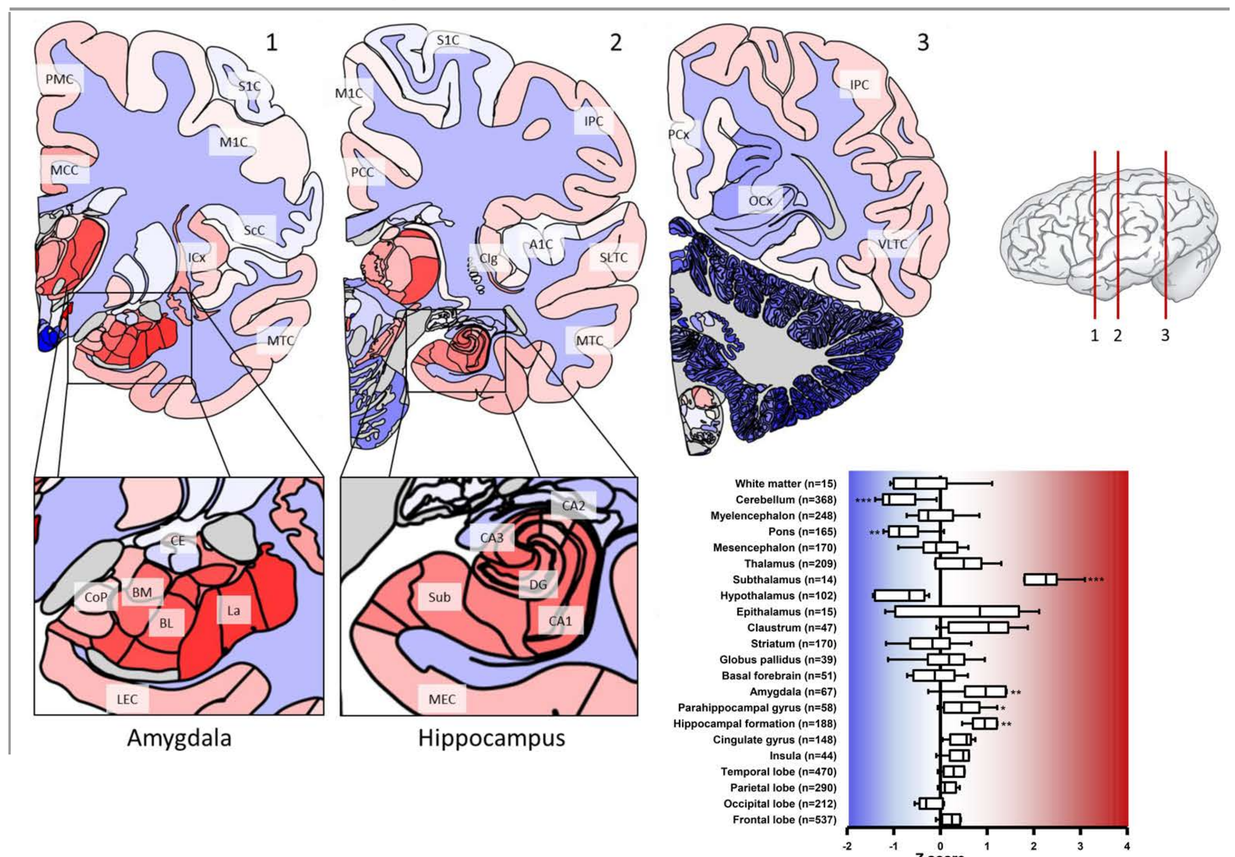


Allen Human Brain Atlas

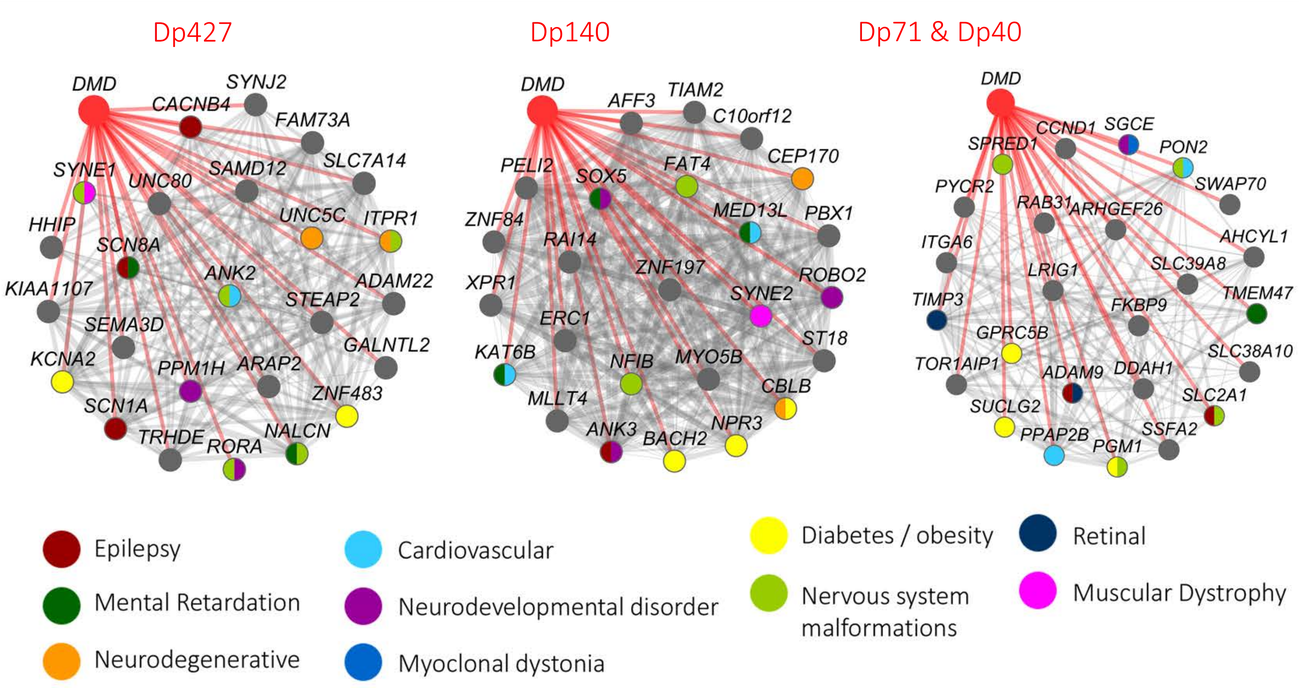
6 adult donors (5 males & 1 female; mean age 42, range 24-57 years)
363 to 946 different samples per brain (3,702 samples in total)
Microarray gene expression (only Dp140bc; no other isoforms)



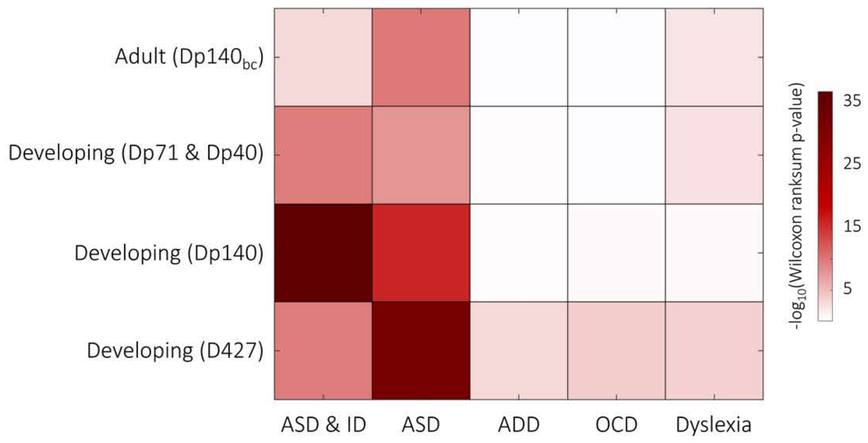
Adult DMD Expression



Association with developmental disorders



Genes co-expressed with DMD are enriched in genes related to ASD & ID



Conclusions

Results of the longitudinal isoform expression suggest that Dp71+Dp40 could be a potential post-natal therapeutic target more than Dp140. The enriched co-expression provides a genetic link that might explain the high incidence of ASD and ID in DMD. Knowledge from these genes may lead to a better understanding of the function of dystrophin in the brain.

References

[1]Miller J a, et al. (2014) Transcriptional landscape of the prenatal human brain. Nature 508(7495):199–206.
[2]Hawrylycz MJ, et al. (2012) An anatomically comprehensive atlas of the adult human brain transcriptome. Nature 489(7416):391–9.

a.mahfouz@lumc.nl