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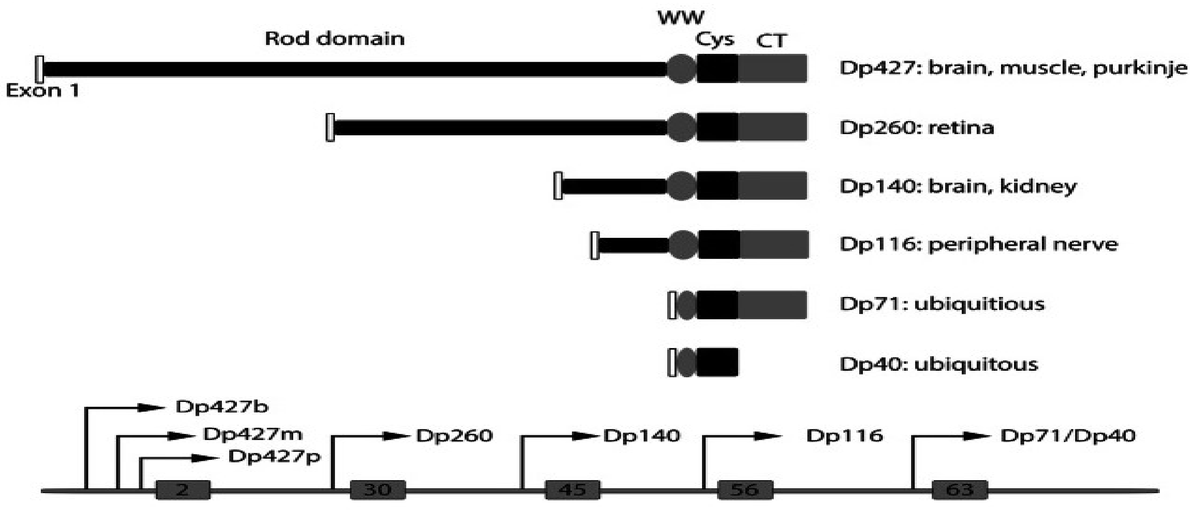
Duchenne muscular dystrophy gene expression is an independent prognostic marker for IDH mutant low-grade glioma

The *DMD* gene and Cancer

- The Duchenne muscular dystrophy (*DMD*) gene is the largest known human gene spanning a genomic range over 2Mb. It encodes multiple protein products of varying size and function [1].
- Several studies have emerged showing that muscular dystrophy mouse models are prone to develop spontaneous soft tissue sarcomas (STS) [2].
- High *DMD* expression has been linked to several cancers, including low-grade glioma (LGG), improving prognosis in some and worsening prognosis in others [2].
- Although literature has previously linked the *DMD* gene to numerous cancers, none have considered the many gene products produced by the *DMD* gene.
- Dp71 is a ubiquitous dystrophin protein and the predominant *DMD* product in the brain [3].

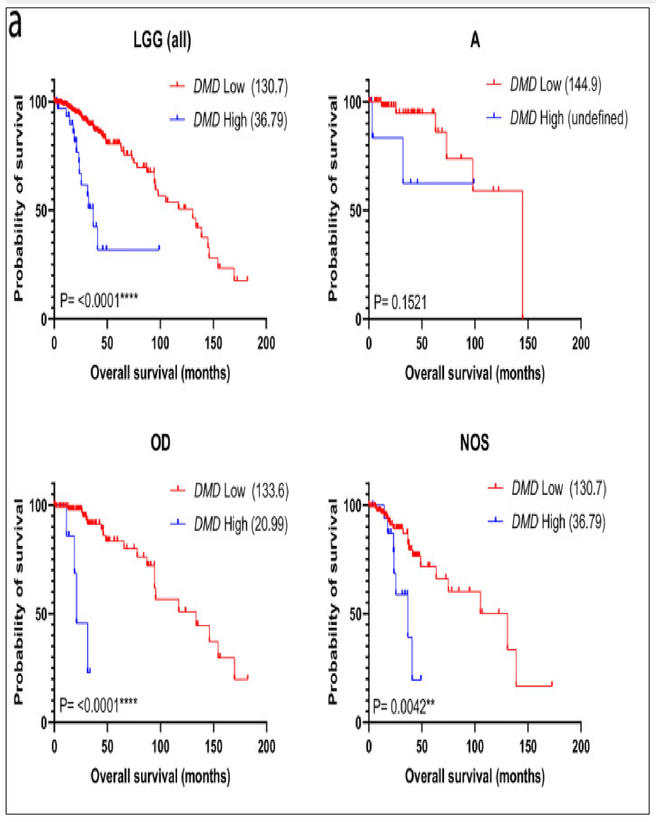


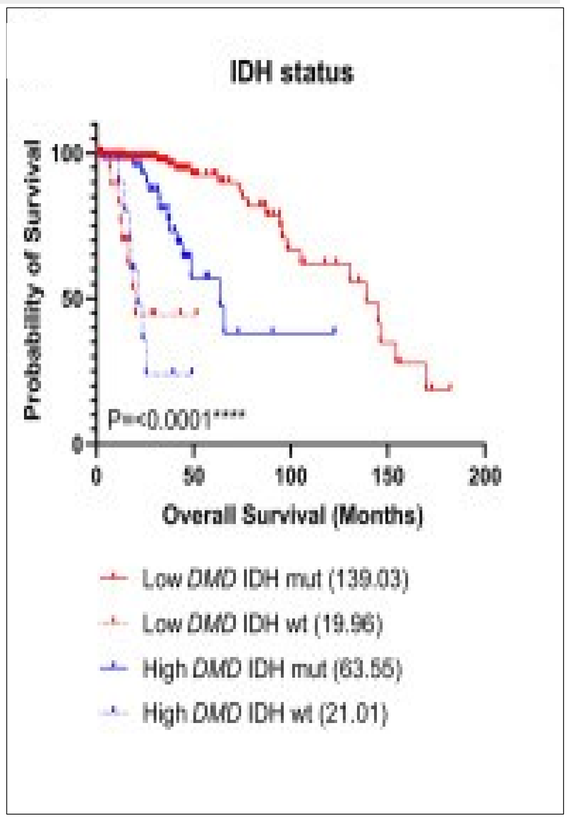
Objectives

- Use *in silico* analysis to investigate the relationship between *DMD* gene expression and LGG survival
- Analyse *DMD* expression in LGG patient tissue using immunohistochemistry

High DMD expression is significantly associated with poor survival in LGG including a subset of IDH mutant patients

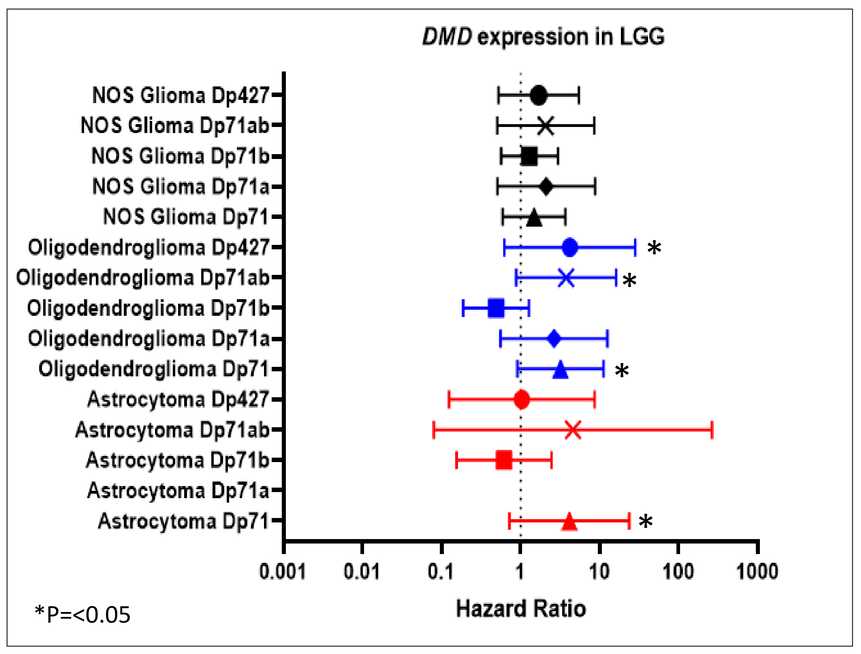
- To explore the association of *DMD* gene expression in LGG, we analysed RNAseq data from an LGG (WHO grade II) TCGA dataset (n=319) using the X-tile software to generate a cut-point, dichotomising the data set into high/low *DMD* expression.
- The median overall survival for the high *DMD* group was 36.79 months compared to 130.7 months for the low *DMD* group, a difference of over 7 years (p=<0.001).
- Survival analysis on each LGG subtype (Astrocytoma n=66, Oligodendroglioma n=117 and NOS n=134) showed that high *DMD* expression was associated with poor survival in each of them with hazard ratios 3.0 (p=0.1521), 9.8 (p=<0.0001) and 3.19 (p=0.0042) respectively.
- High *DMD* expression was associated with poor survival in IDH mutant cases but not wt.





The expression of multiple *DMD* gene products are significantly associated with LGG survival outcomes

- Dp71 isoforms (Dp71, Dp71a, Dp71b and Dp71ab) and Dp427m are the most abundant in LGG tissue
- High expression of the Dp71, Dp71ab and Dp427m gene products were significantly associated with poor LGG survival

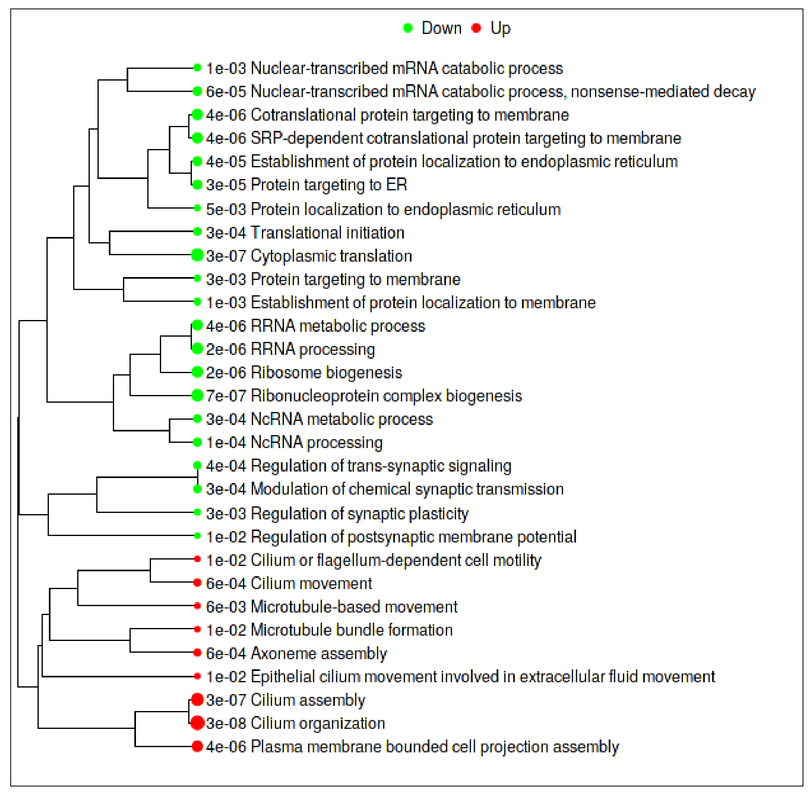


DMD Pathway analysis using GAGE method

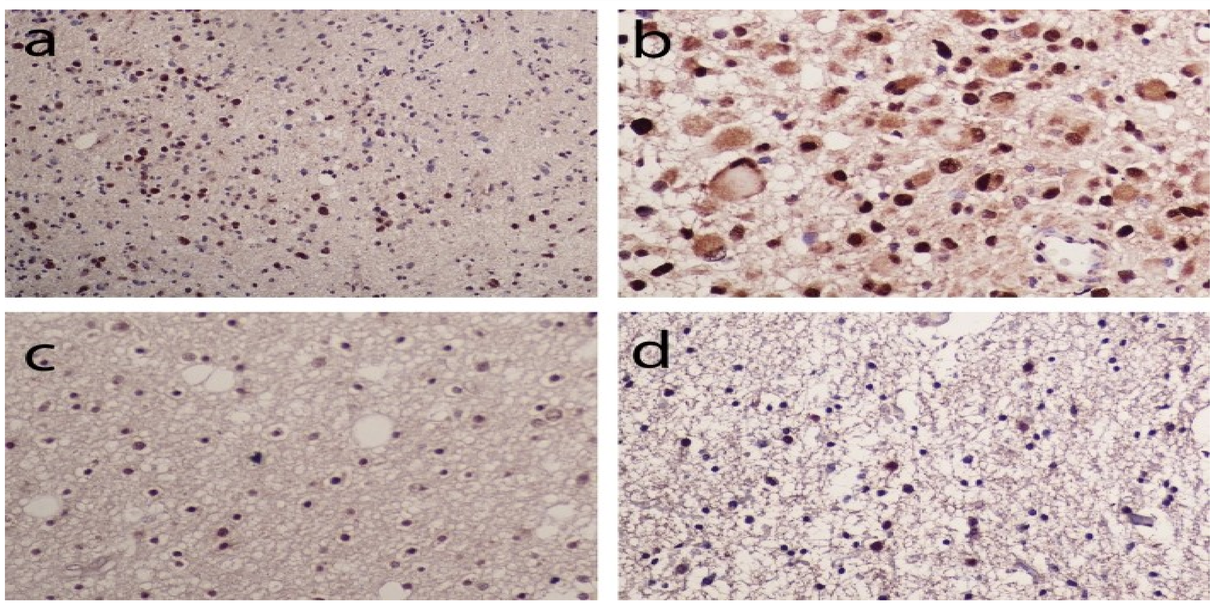
Differential gene expression analysis was done on *DMD* high/low cases using IDEP.

Pathway analysis reveals that *DMD* expression down regulates cytoplasmic translation and ribosome biogenesis, and upregulates cilium organisation and assembly, and plasma membrane-bounded cell projection assembly

(Sizes of dot correspond to adjusted P values)



DMD products are expressed in the cytoplasm and nucleus of glial cells in LGG



We conducted a pilot immunohistochemistry study on a small cohort of 24 LGG cases (18 astrocytoma, one oligodendroglioma and five NOS) using a pan-dystrophin antibody. Nine out of the 24 cases were IDH mutant and 15 were IDH wild-type. Dystrophin expression was observed in both the cytoplasm and nucleus of glial cells within LGG.

Summary

- The expression of the individual *DMD* gene products Dp71, Dp71ab and Dp427 are significantly associated with overall survival in LGG which have differential biological effects relevant to the pathogenesis of LGG.
- The *DMD* gene may represent a novel target for therapeutic intervention in LGG.

References

1. Naidoo, M., Jones, L., Conboy, B., Hamarneh, W., D'Souza, D., Anthony, K. and Machado, L.R. (2022). Duchenne muscular dystrophy gene expression is an independent prognostic marker for IDH mutant low-grade glioma. *Scientific Reports*, [online] 12(1). doi:10.1038/s41598-022-07223-2.
2. Jones, L., Naidoo, M., Machado, L. R. & Anthony, K. Te Duchenne muscular dystrophy gene and cancer. Cell. Oncol. 1, 19–32 (2020)
3. Naidoo, M. & Anthony, K. Dystrophin Dp71 and the neuropathophysiology of Duchenne muscular dystrophy. Mol. Neurobiol. 57, 1748–1767 (2020).