The Relationship between Dystrophin Brain Isoforms, Motor Outcomes and Age of Diagnosis in Children and Young Adults with Duchenne Muscular Dystrophy

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INTRODUCTION

Duchenne Muscular Dystrophy (DMD) is caused by *DMD* mutations leading to loss of the dystrophin protein. In addition to the universal involvement of the muscle isoform Dp427, the site of the *DMD* mutation might lead to the additional involvement of two isoforms expressed in brain, Dp140 and Dp71, with consequences for brain function.

Our aim is to determine whether mutations affecting the different dystrophin isoforms affect the motor function of boys with DMD.

METHODS

The NorthStar Ambulatory Assessment (NSAA) is a scale of motor function. Clinical information for 753 DMD participants aged 4.0 to 21.8 years was classified by *DMD* mutation effects on isoform expression as follows; group 1 (Dp427 absent, Dp140/Dp71 present, n=299); group 2 (Dp427 absent, Dp140 unknown and Dp71 present, n=182); group 3 (Dp427/Dp140 absent, Dp71 present, n=226); and group 4 (Dp427/Dp140/Dp71 absent, n=46).

RESULTS 1

For all ages, there were significantly lower NSAA scores in those lacking shorter brain dystrophin isoforms (groups 3 and 4), with a cumulative effect of loss of isoforms: NSAA lower in group 3 than group 1 ($p<0.001$), NSAA lower in group 4 than group 1 ($p<0.00001$) and NSAA lower in group 4 than group 3 ($p<0.01$).

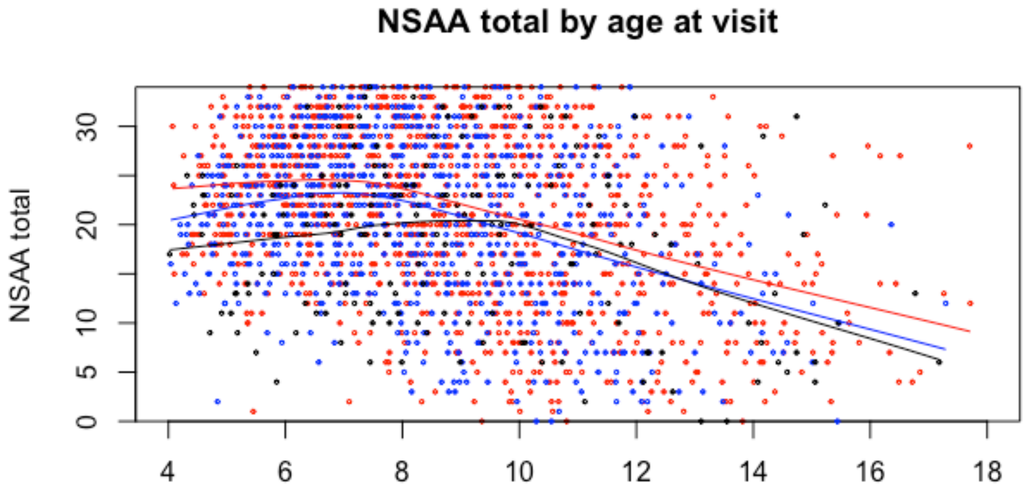

Fig 1 NSAA total scores by age at visit in 3 different groups: group 1 (Dp140+Dp71+, red), group 3 (Dp140-Dp71+, blue) and group 4 (Dp140-Dp71-, black). The lines represent the loess regression curve for NSAA total scores by age in the different groups.

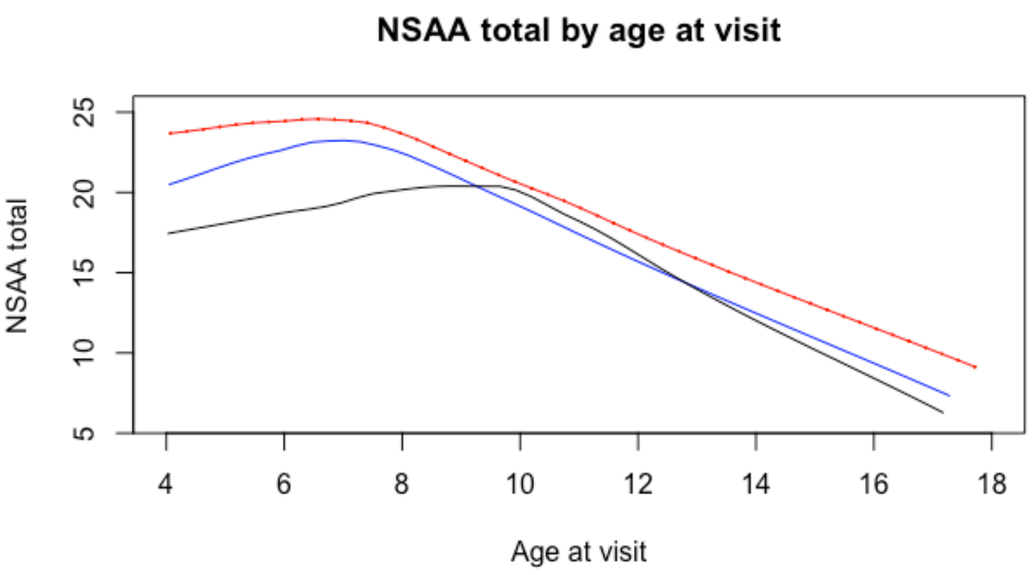

Fig 2 NSAA total scores by age at visit in 3 different groups: group 1 (Dp140+Dp71+, red), group 3 (Dp140-Dp71+, blue) and group 4 (Dp140-Dp71-, black). The lines represent the loess regression curve for NSAA total scores by age in the different groups. Loess regression curves shown only

RESULTS 2

Peak NSAA scores occurred later and were lower in groups 3 and 4: 23 at 7.0 years (group 3) and 20 at 8.9 years (group 4) versus 25 at 6.6 years (group 1).

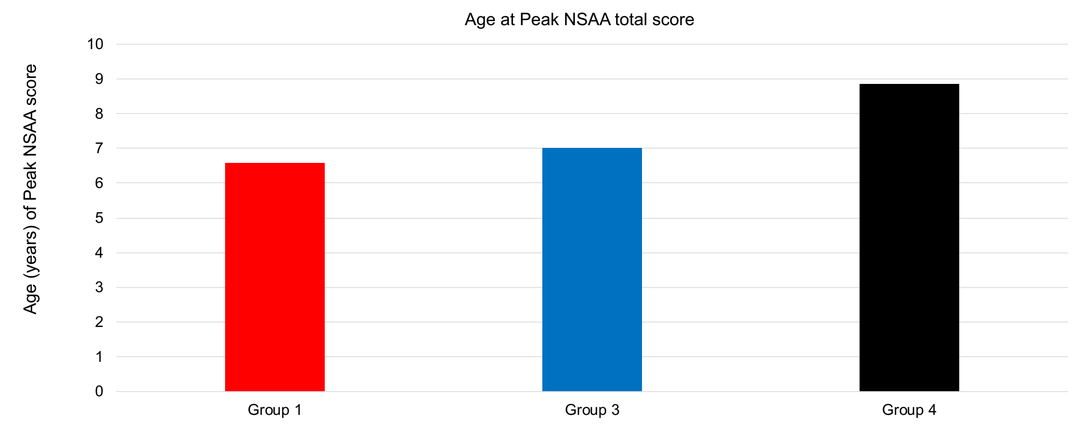

Fig 3 Age (years) at which peak NSAA scores occurred in loess regression model for group 1 (Dp140+Dp71+), group 3 (Dp140-Dp71+) and group 4 (Dp140-Dp71-).

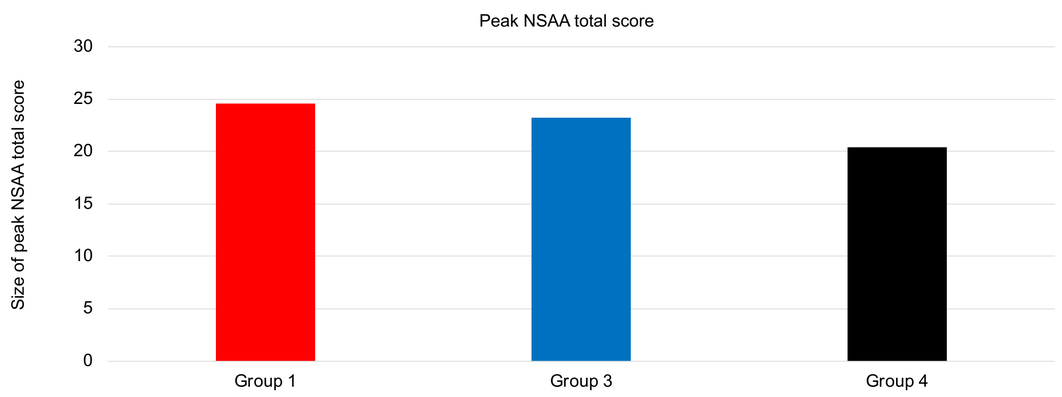

Fig 4 Peak NSAA scores in loess regression model for group 1 (Dp140+Dp71+), group 3 (Dp140-Dp71+) and group 4 (Dp140-Dp71-).

For all ages, rise from supine times were also significantly slower in those lacking shorter brain dystrophin isoforms (groups 3 and 4), with a cumulative effect of loss of isoforms. Rise times were slower in group 3 than group 1 ($p<0.04$), slower in group 4 than group 1 ($p<0.01$) and slower in group 4 than group 3 ($p<0.02$).

Those lacking brain dystrophin isoforms had an earlier median age of diagnosis ($p<0.02$): 3.2 years (group 4), 4.0 years (group 3) and 4.2 years (group 1).

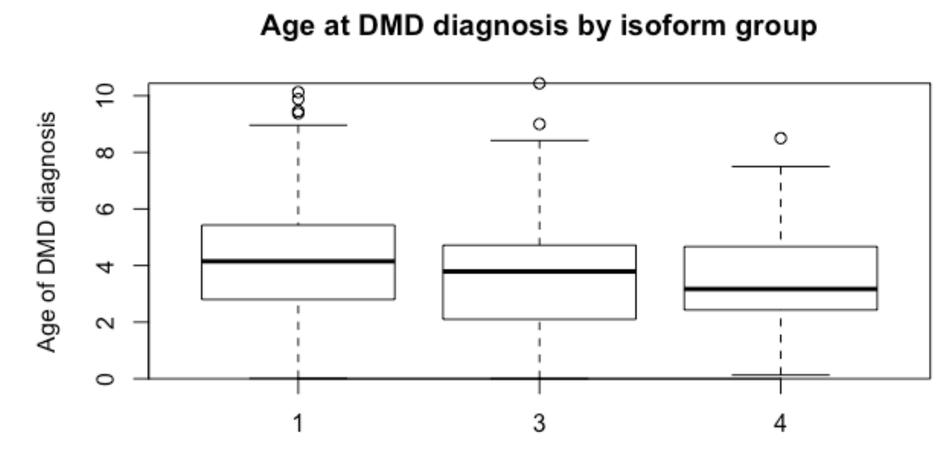

Fig 5 Age of DMD diagnosis box plot for group 1 (Dp140+Dp71+), group 3 (Dp140-Dp71+) and group 4 (Dp140-Dp71-).

Note – results for group 2 not shown in figures 1-5 for clarity as DMD mutation effects on Dp140 expression are unknown in this group.

CONCLUSION

In addition to the known CNS phenotype, DMD boys lacking brain dystrophin isoforms exhibit worse motor outcomes and are diagnosed at an earlier age, most markedly in those lacking both Dp140 and Dp71. This has important implications for patient prognostication and clinical trial design. These are preliminary results of an ongoing project investigating the relationship between dystrophin isoforms and motor outcomes in DMD.

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