Effects of Genetic Variants on Lower Leg Muscle Fat Fraction Evaluated with MRI in Becker Muscular Dystrophy

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INTRODUCTION

- Becker muscular dystrophy (BMD) is characterized by variants in DMD gene, leading to partial production of dystrophin or altered size of the protein.[1,2]
- BMD variants maintain the open reading frame and are associated with a wide variety of phenotypes.[3,4,5]
- Studies have shown genotypic-phenotypic relationship where specific variants can affect severity of disease progression and age at loss of ambulation.[6,7,8,9]
- Some deletions of specific exons, such as del "x-51" & "48", have shown less disease involvement compared to del 45-x.[10]
- There is limited knowledge of how muscle fat fraction (FF) measured with MRI is related to genetic variants in BMD. Gaining a better understanding of this relationship will aid in defining the prognosis for specific subsets of BMD and be valuable for future therapeutic developments.

AIM

- To examine FF of lower leg muscles measured with MRI in individuals with different genetic variants of BMD

METHODS

Subjects

- We recruited ambulatory (n=24) and non-ambulatory (n=5) participants with BMD (n=29; age:19-65 years) between Dec 2021-January 2025 and evaluated their dominant leg using 3-T MR systems.
- Genetic reports were used to determine the genetic variant of the individuals with BMD (Fig. 1).

MRI

- Three-point Dixon images were acquired from the lower leg using a 3T Philips MR system during an ImagingNMD study visit held at the UF AMRIS Facility.

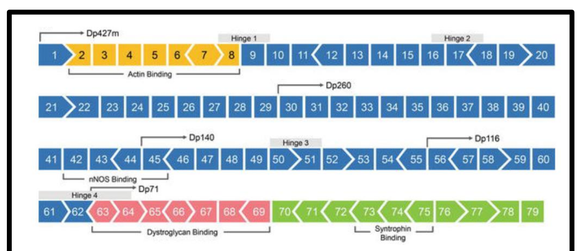

Fig 1. DMD gene (adapted from ref 11).

- Reconstructed FF maps were derived, ROI's of individual muscles drawn, and comparisons among muscles and different genetic variants were performed using one-way ANOVA. Also, the relationship of age and FF was examined.

Table 1: Participant characteristics; variants, ambulatory status, number of participants (n), average age (standard deviation; SD).

Variant group	Variant	Ambulatory status	n	Average age (SD)
Large Del		WC=6	24	37.9 (12.9)
	45-47	WC-4 Amb-3	7	43.2 (13.06)
	45-48	Amb	4	34 (14.16)
	49-51	Amb	2	39.5 (10.6)
	48-51	Amb	2	46.5 (21.9)
Single/small Del		Amb	2	34.6 (9.19)
Splice site		Amb	2	21.5 (3.5)
Duplication		Amb	1	44
Total			29	

RESULTS

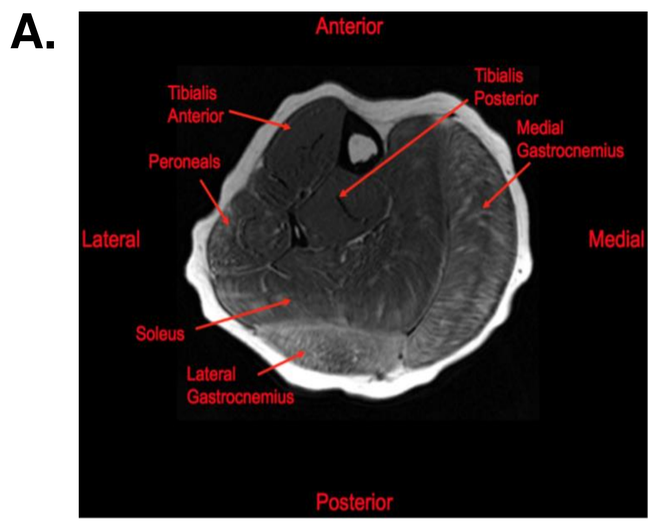

Figure 2. A) MRI dixon fat image showing muscles of interest. B) Differences among muscles were observed with the MG and LG being most involved and the TA and TP being more preserved.

RESULTS (Con't)

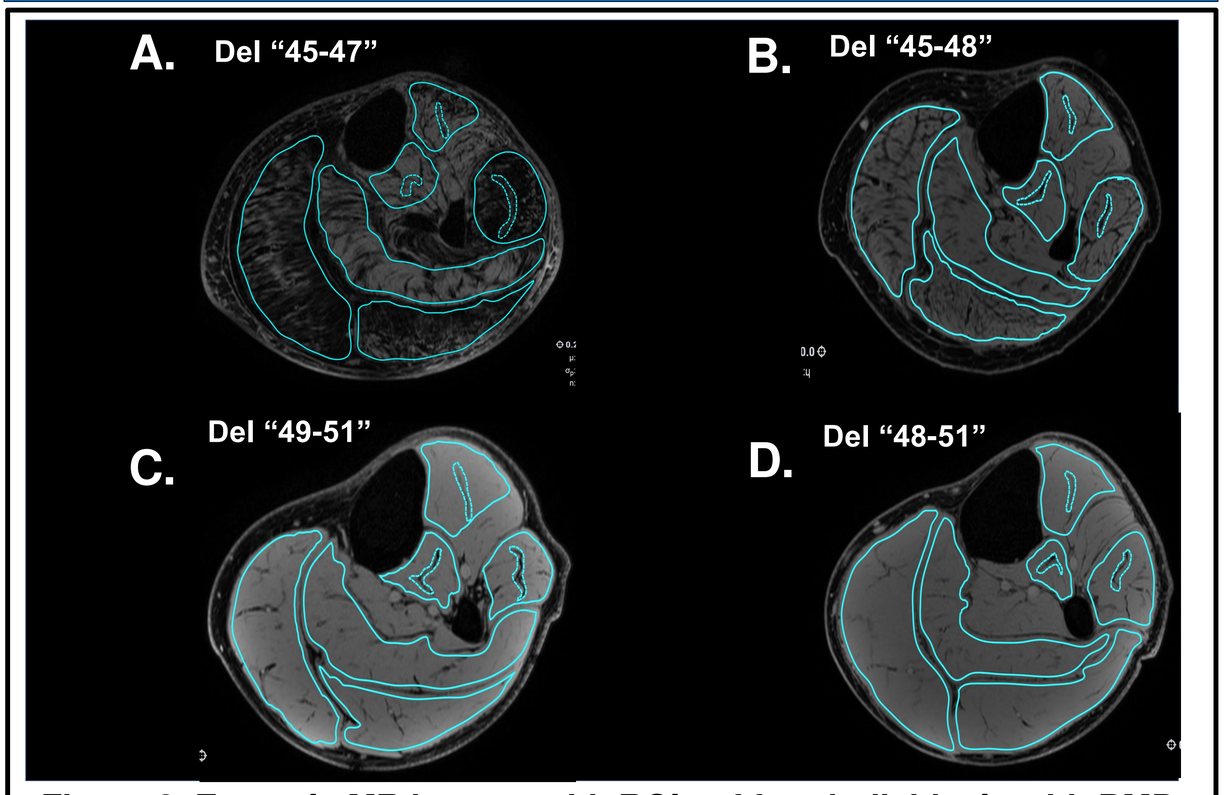

Figure 3. Example MR images with ROIs of four individuals with BMD with different genetic variants. Note, individual with Del 45-47 tends to show most involvement.

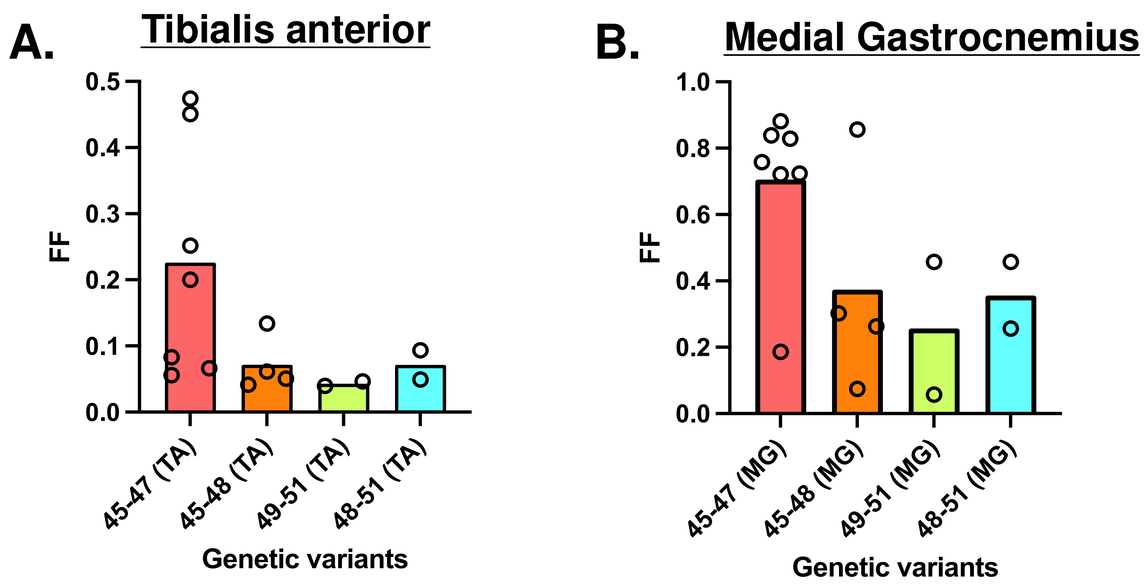

Figure 4. Comparison of genotype variant in the tibialis anterior (A) and medial gastrocnemius (B) muscles of individuals with BMD.

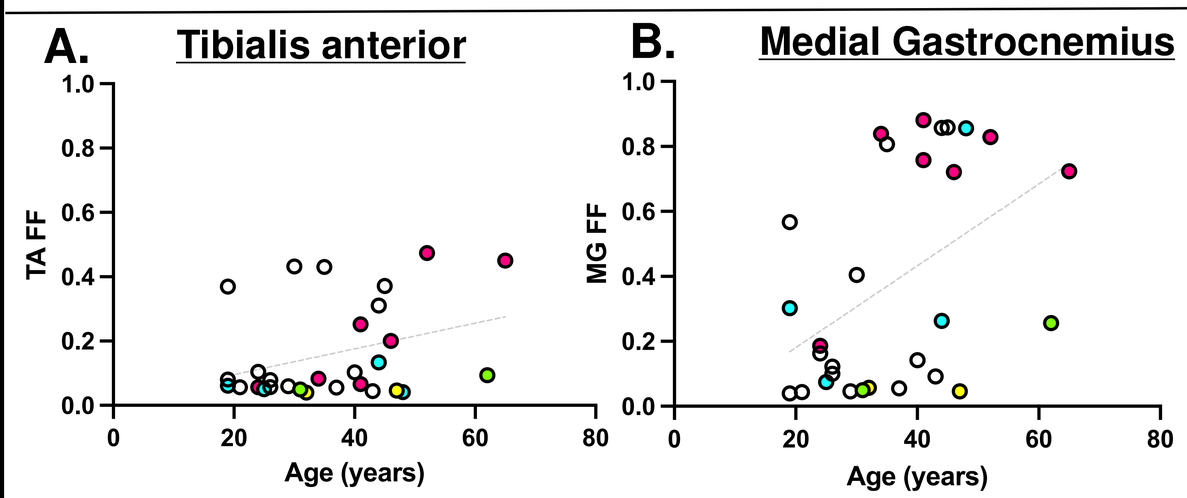

Figure 5. Scatter plots showing a weak/moderate relationship of FF and age in the tibialis anterior (A; r^2=0.10) and medial gastrocnemius (B; r^2=0.21) of individuals with BMD.

CONCLUSIONS

- Our findings are consistent with exon del "45-47" being a more severe phenotype compared to exon "45-48" and exon "x-51" deletions, in agreement with functional data in recent papers.
- These findings support that MRI FF is a valuable tool for non-invasively evaluating genetic variants in BMD, and they provide insight into exon skipping therapeutic approaches in Duchenne muscular dystrophy.

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