

Alpha-Dystroglycan Glycosylation in Heterozygous FKRP Carriers of LGMDR9

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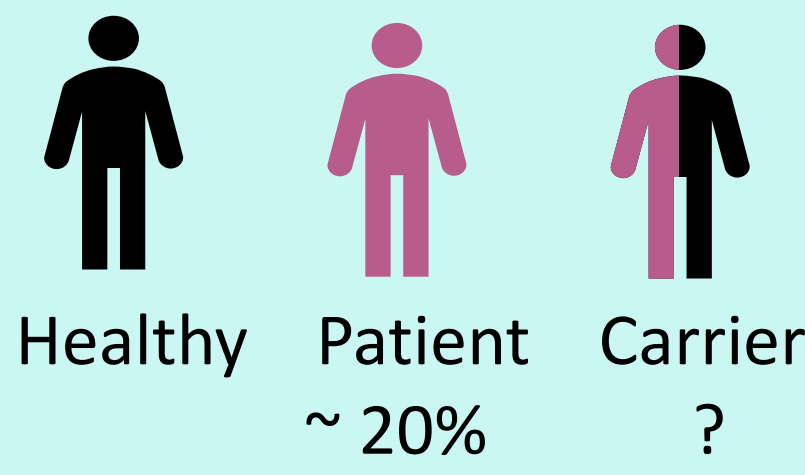
BACKGROUND

Limb-girdle muscular dystrophy type R9 (LGMDR9) is caused by pathogenic variants in the *FKRP* gene. *FKRP* encodes fukutin-related protein (FKRP), an enzyme responsible for glycosylation of alpha-dystroglycan (αDG) and essential for muscle fiber integrity and function. In patients, αDG glycosylation levels are reduced to around 20% of normal, resulting in progressive muscle weakness and loss of function.

Heterozygous carriers remain clinically asymptomatic, but their αDG glycosylation has not been systematically quantified. The minimal glycosylation threshold required for normal muscle function remains unknown and represents a key target for therapeutic in LGMDR9.

AIM

To quantify αDG glycosylation in asymptomatic heterozygous *FKRP* carriers



METHODS

- 34 carriers with different *FKRP* variants were recruited through family members of patients with LGMDR9.
- Biopsies of the left tibialis anterior (TA) muscle were obtained and analyzed using a validated multiplex fluorescent Western blot assay to quantify glycosylated αDG¹.
- A representative normal donor TA reference standard served as source tissue for calibration curve and quality control.

RESULTS

	c.1384C>T P462S (N=2)	c.469G>C A157P (N=1)	c.826C>A L276I (N=31)	Overall (N=34)
Age				
Median [range]	50.5 [40; 61]	62 [62; 62]	57 [19; 68]	58 [19; 68]
Sex				
Female	1 (50%)	1 (100%)	15 (48.4%)	17 (50%)
Male	1 (50%)	0 (0%)	16 (51.6%)	17 (50%)
BMI				
Median [range]	27.3 [26.9; 27.6]	22.9 [22.9; 22.9]	25.9 [20.3; 32.9]	26 [20.3; 32.9]

Table 1. Baseline characteristics of *FKRP* heterozygous carriers.

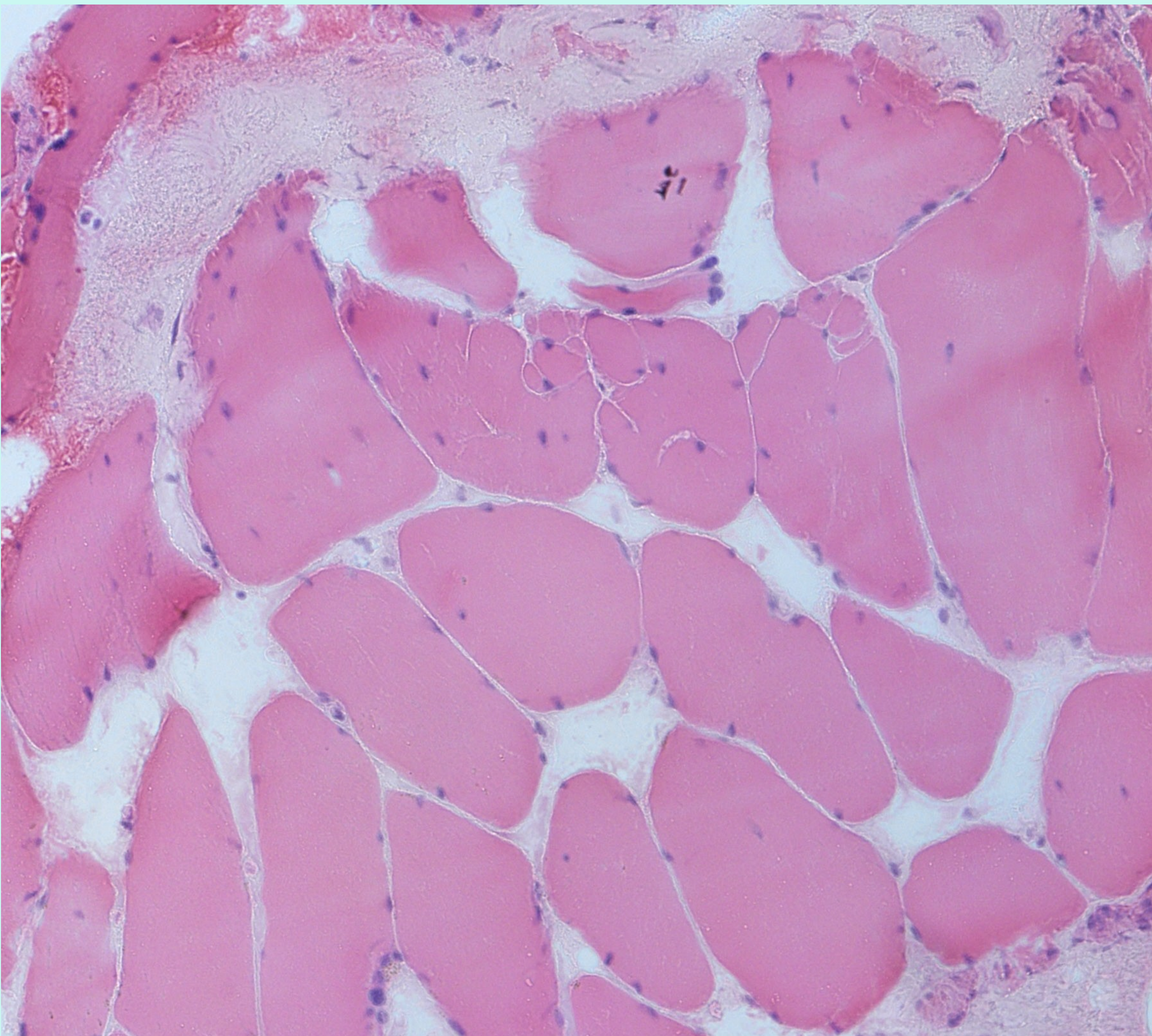
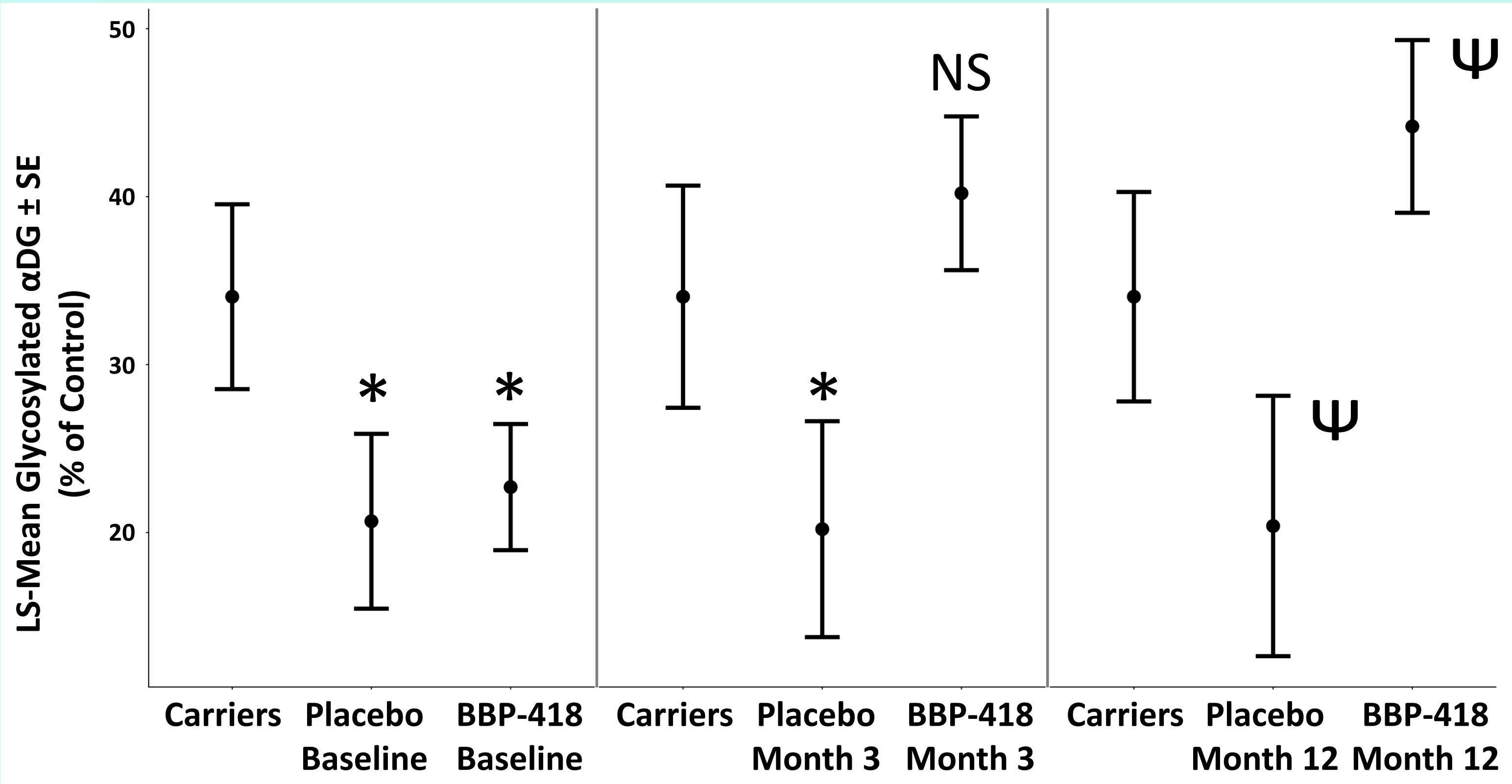


Figure 2. Several carriers show centralized nuclei and fiber size variability in muscle biopsies.

Figure 1. Glycosylated αDG levels in patients with LGMDR9 treated with BBP-418 compared to carriers of *FKRP* variants. Patient data derived from the Phase 3 FORTIFY study². BBP-418 = treatment group; LS=least squares; SE=standard interim analysis error; * = p<0.001 compared to carriers.; ψ = p<0.05 compared to carriers.; NS = not significant compared to carriers. Statistical comparisons performed using Wilcoxon test and LS-means pairwise comparisons (linear model).

TAKE HOME MESSAGE

- Carriers of *FKRP* variants showed significantly reduced αDG glycosylation vs. controls.
- Carriers exhibit signs of muscle regeneration on biopsies but are clinically unaffected.
- BBP-418 treatment increased mean glycosylated αDG to carrier levels by month 3, and the level of glycosylated protein was sustained through month 12.



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