Female carriers of BMD and DMD mutations show elevated muscle injury proteins, and muscle loss progression is predicted by plasma ART3 concentration

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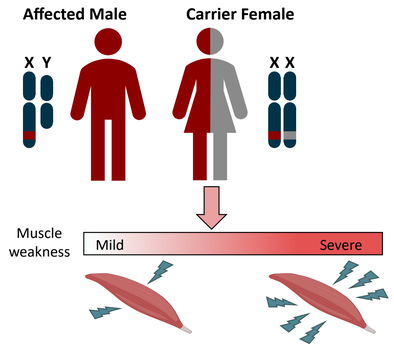
Conclusion

- BMD and DMD carriers show significant proteomic differences from healthy individuals and proteomic evidence of skeletal muscle injury.
- Elevated skeletal muscle injury is higher in DMD than BMD carriers, and is associated with elevated muscle fat, reduced strength, and reduced ART3.
- Reduced ART3 is correlated with more thigh muscle fat fraction (TMFF) change at follow-up.
- ART3 may serve as a predictive biomarker for progressive fat replacement and loss of muscle strength.

Background

Duchenne (DMD) and Becker muscular dystrophy (BMD) are X-linked recessive disorders resulting from genetic variants in the dystrophin gene and are characterized by progressive muscle degeneration and functional loss. While affected individuals are primarily male, ~5-20% of female carriers exhibit clinical manifestations such as muscle weakness, which may range from mild to severe.[1]



Muscle tissue injury following contraction causes the release of proteins into circulating blood. We previously identified plasma proteins that are indicative of contraction-induced skeletal muscle injury, such as fast skeletal troponin I (TNNI2) and creatine kinase (CK), using the SOMAscan proteomics platform.[2]

We hypothesized that plasma proteomic signatures reflecting muscle injury would differ between carriers and healthy controls and that longitudinal profiling could identify proteins that correlate with or predict functional changes over time.

Methods

Baseline plasma samples were collected from 22 DMD carriers, 14 BMD carriers, and 21 healthy volunteers (HV), and plasma proteomics were analyzed using the SOMAscan 7K platform. Longitudinal samples (mean 6.5 yr follow-up) were obtained from 12 DMD and 8 BMD carriers. Thigh muscle fat fraction (TMFF; DMD n=31; BMD n=22) was measured by muscle MRI, and muscle strength was assessed using Medical Research Council Muscle Strength Scores (MSS) (DMD n=15; BMD n=8).

Demographics			
	BMD	DMD	HV
# Participants	14	22	21
Age (Mean years ± STD)	52.8 ± 13.3	54.4 ± 13.3	48 ± 12.4
MSS Score (Mean ± STD)	97.9 ± 4.87	98.4 ± 2.55	
Muscle Weakness (MSS < 100)	5 (35.7%)	12 (44.4%)	
TMFF % (Mean ± STD)	10.8 ± 4.68	18.4 ± 19.2	

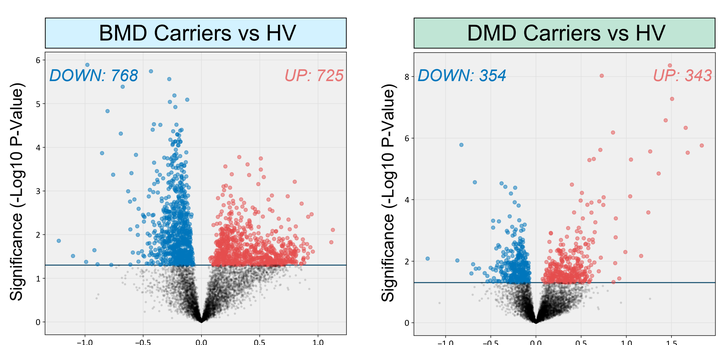
Plasma Sample Collection			
	Baseline	6.5 years	Follow-up
BMD	14	→	8
DMD	22	→	12

Total Samples	
BMD	22
DMD	34
HV	21

→ SOMAscan 7K Assay

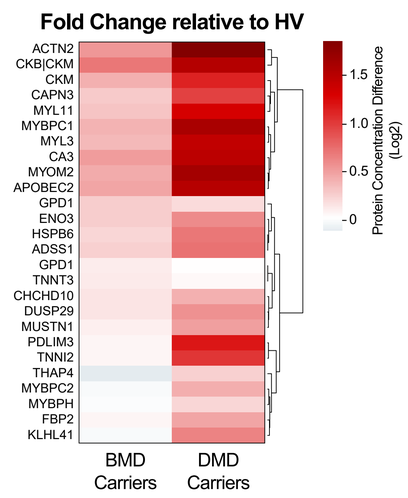
Results

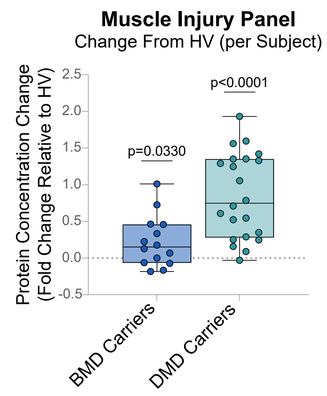
BMD and DMD carriers exhibit significant proteomic differences from HV



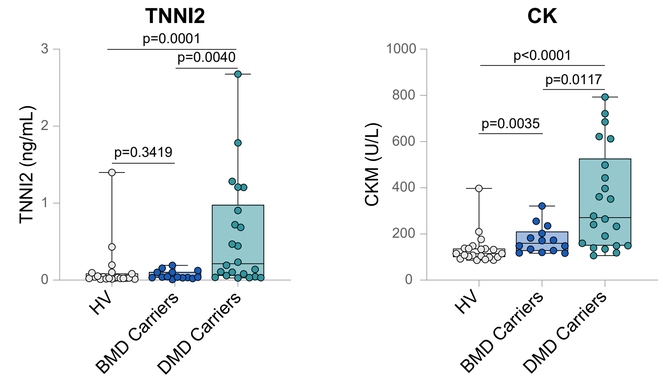
Results

Skeletal muscle injury proteins are elevated in carriers at baseline relative to HV

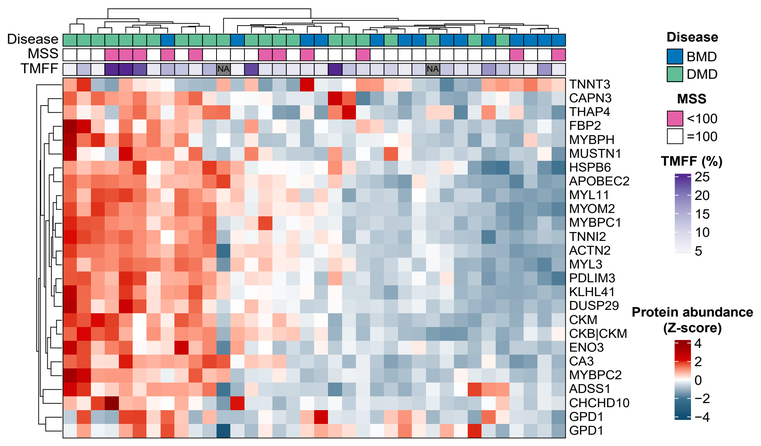




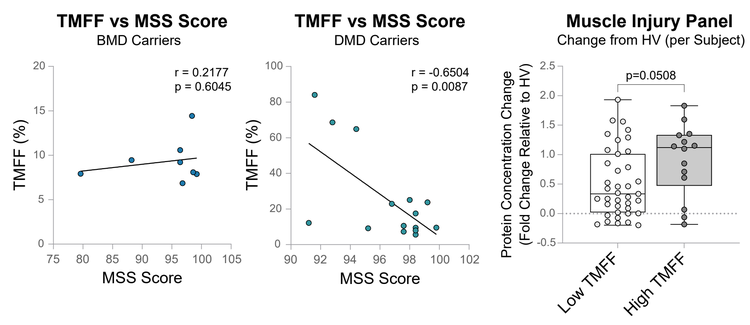
TNNI2 and CK are differentially elevated in BMD and DMD carriers at baseline



Carriers' profiles cluster into high and low muscle injury groups at baseline

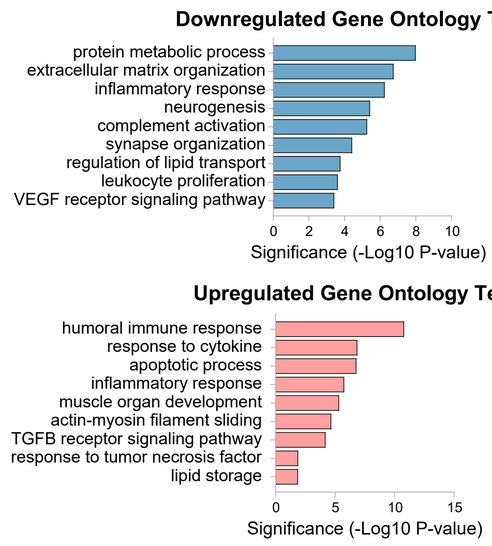


Greater TMFF correlates with reduced MSS score and elevated muscle injury signature

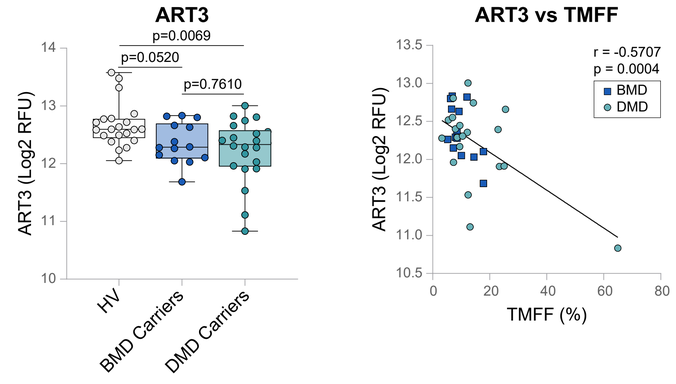


Results

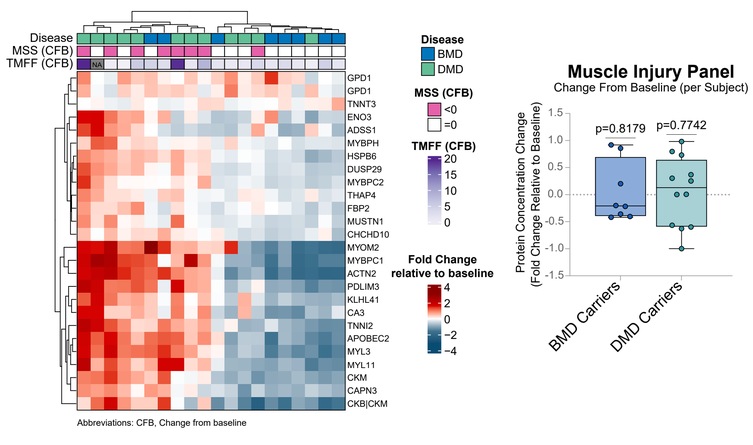
Gene Ontology enrichment analysis of differentially regulated proteins in high TMFF carriers



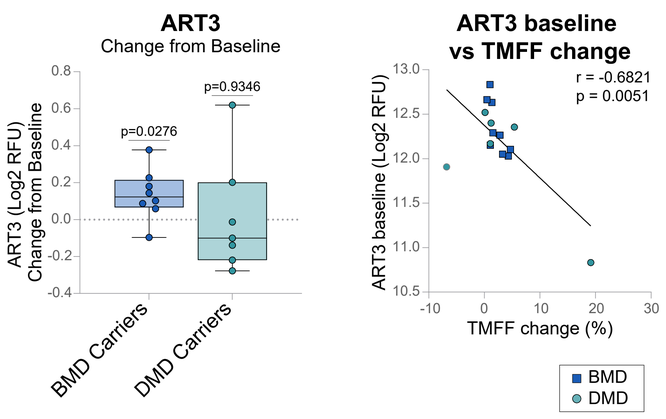
ART3 levels are lower in carriers relative to HV at baseline, and is associated with TMFF



A subset of carriers show changes in muscle injury signature at follow-up



ART3 levels decrease in a subset of carriers and baseline levels are correlated with TMFF change



References

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2. Stemmerik, M. G., Barthel, B., Andersen, N. R., Skriver, S. V., Russell, A. J., & Vissing, J. (2025). Universal Proteomic Signature After Exercise-Induced Muscle Injury in Muscular Dystrophies. Annals of clinical and translational neurology, 12(5), 998–1011.

Disclosures

Luuli Tran, Ben Barthel, Alan J Russell are shareholders and employees of Edgewise Therapeutics.

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