A Low AAVrh74 Seroprevalence Is Observed in Adults with Facioscapulohumeral Muscular Dystrophy (FSHD)

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INTRODUCTION

- Adeno-associated virus serotype rh74 (AAVrh74) is considered a leading vector to deliver therapeutic cargo in neuromuscular diseases
- Humoral pre-existing immunity (PEI) to AAVs is a key consideration for in vivo AAV gene delivery, as it may diminish the potential benefit-to-risk profile.
- The AAVrh74 PEI prevalence has been published in Duchenne muscular dystrophy (DMD) patients[1,2].
- However, the DMD population's young age and chronic glucocorticoid steroid exposure hinder extrapolating the findings to an adult population with competent immunity, such as most patients with symptomatic Facioscapulohumeral muscular dystrophy (FSHD).
- To address this knowledge gap, a cross-sectional observational study was conducted with the primary objective to better understand the seroprevalence for AAVrh74 in adults with symptomatic FSHD.
- The data gathered from this study are expected to aid in the clinical development of EPI-321, a single AAVrh74 vector encoding an ultracompact, catalytically inactive Cas protein fused to gene-suppressing modulators, and a guide RNA targeting the DUX4 locus, as a potential one-time therapy for FSHD.

METHODS

- A multi-center, cross-sectional, observational study was conducted at 4 sites in the United States, and at 1 site in New Zealand **(Figure 1**).

Figure 1. Clinical Site Map across United States of America and New Zealand

Study Population:
Inclusion Criteria:
1. Participant age ≧ 18-years.
2. Participant has a diagnosis of FSHD Type 1 as determined by the Investigator.
3. Participant can provide informed consent.

Exclusion Criteria:
1. Participant has a contra-indication to blood draw.

METHODS (continued)

AAVrh74 Total Antibody Binding Assay

- Anti-AAVrh74 antibodies are detected in patient serum using a validated bridging immunogenicity assay.
- The Meso-Scale Discovery (MSD) High Bind plate is coated with unlabeled AAVrh74 to capture anti-AAVrh74 antibodies **(Figure 2)**.
- Ruthenylated-AAVrh74 is used to detect captured antibodies using an MSD S600 plate reader **(Figure 2)**.
- The presence of anti-AAVrh74 antibodies is determined by comparing the luminescent signal in the sample or control to a statistically derived threshold, the assay cut point.

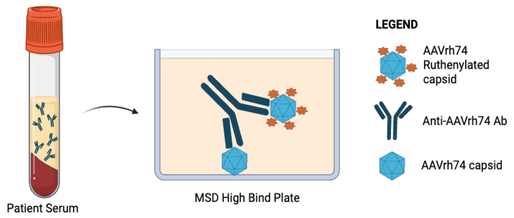

Figure 2. Visualization of the AAVrh74 Total Antibody Binding Assay

- Participants with titers ≧ 1:400 were classified as having pre-existing immunity to AAVrh74 .

Participants' Demographic and Medical History Characteristics

- Date of birth and biological gender at birth were collected.
- Other FSHD 1 disease-specific data collected were age at FSHD Type 1 Diagnosis, date of first signs or symptoms of FSHD, Ricci FSHD Clinical Severity Score and number of D4Z4 repeat units of the contracted allele.
- Data were summarized using descriptive statistics.

RESULTS

- There were a total of 58 participants in this study **(Table 1).**

Characteristics	Mean, SD/%
Age (years), mean ± SD	46 ± 16.3
Female, n (%)	33 (56.9)
Confirmed FSHD Type 1 Diagnosis, n (%) Yes Yes (in a relative) Unknown	 55 (94.8) 1 (1.7) 2 (3.4)
Age of FSHD Type 1 symptom onset (years), mean ± SD	23.3 ± 17.1
Ricci score (5-point scale), mean ± SD	3 ± 1.1
D4Z4 repeat unit length known, n (%) Yes No	 55 (94.8) 3 (5.2)
D4Z4 repeat unit length, mean ± SD	5.2 ± 1.7

RESULTS (continued)

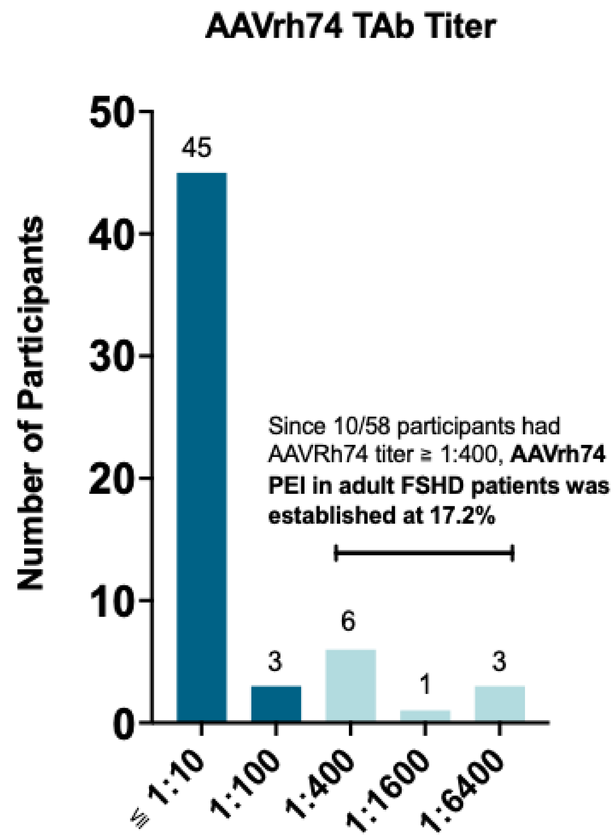

Figure 3. Number of Participants at AAVrh74 Total Antibody Titer tiers

CONCLUSIONS

- 10/58 (~17%) participants were seropositive for AAVrh74 per the study criterion.
- The observed low PEI among adults in this study highlights the potential of AAVrh74 as an appropriate gene delivery vector for FSHD.
- The first-in-human study of EPI-321 for FSHD is ongoing, and clinical data are expected in 2026 (ClinicalTrials.gov ID NCT06907875)

REFERENCES

1. Goedeker NL et al, Ther Adv Neurol Disord. 2023, PMID: 36710722
2. Verma S et al, Hum Gene Ther. 2023, PMID: 36324212

ACKNOWLEDGEMENTS

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