IMPROVING GENE THERAPY FOR LGMDR1/2A PATIENTS

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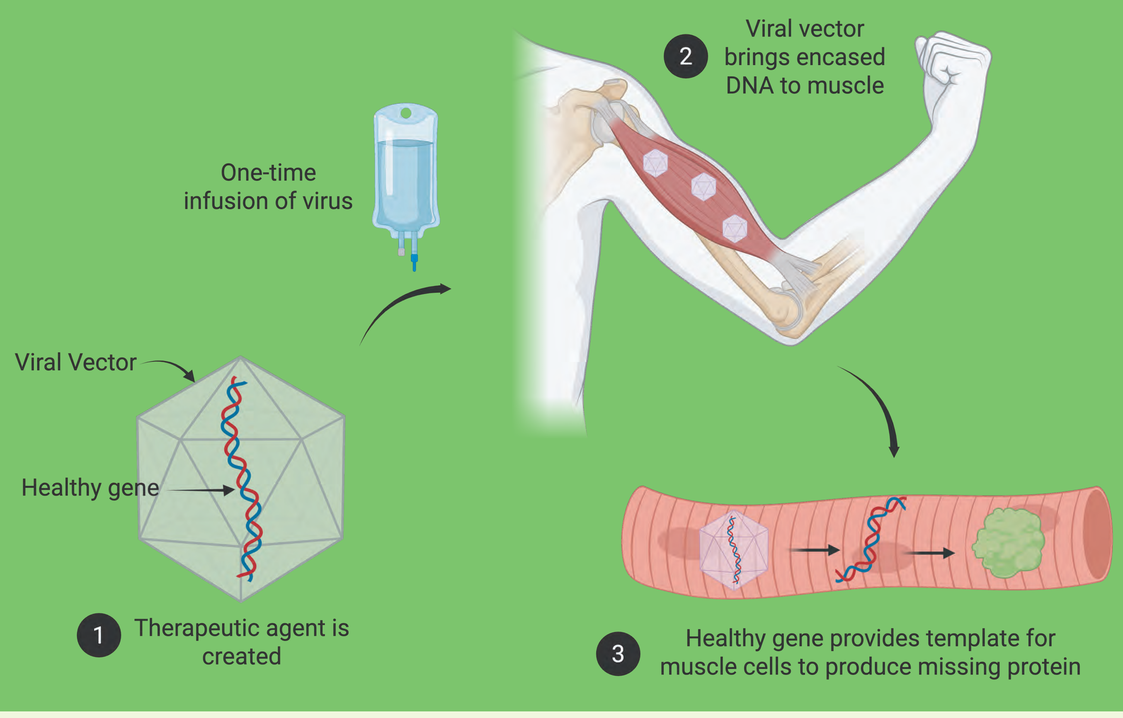
BACKGROUND

Limb-girdle muscle dystrophy type R1/2A (LGMDR1/2A) is caused by mutations in the calpain 3 protein, leading to its absence or dysfunction in affected individuals. Calpain 3 is only found in skeletal muscle, distinguishing LGMDR1/2A patients from other muscle dystrophy patients with heart symptoms.

MOTIVATION

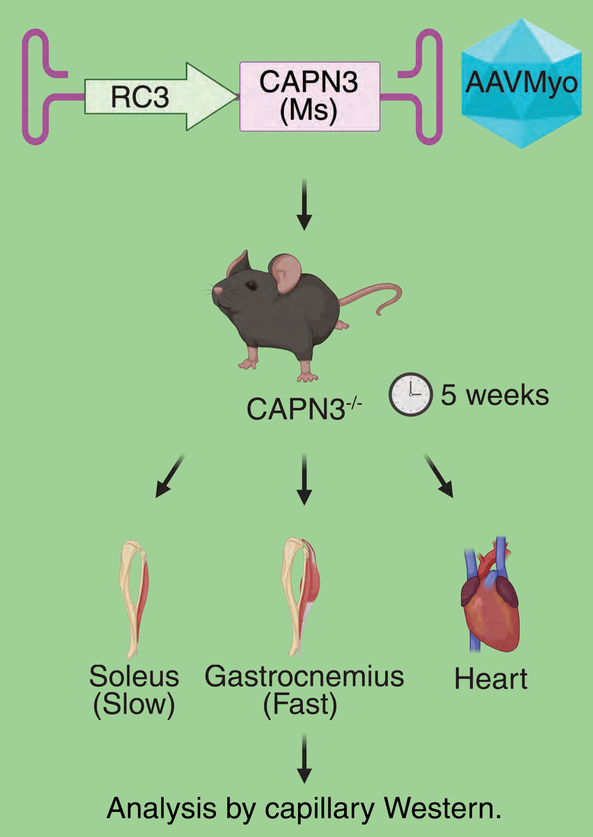
Currently, there are no treatments for patients with LGMDR1/2A. Preclinical research has shown that gene therapy can be used to replace the missing protein in LGMDR1 mice. However, we believe that improvements can be made to enhance the treatment and minimize complications.

HOW GENE THERAPY WORKS



Objective: Develop a new LGMDR1 gene therapy that restores calpain 3 protein in all muscle cells while remaining inactive in the heart.

METHODOLOGY



We examined our gene therapy methods in our LGMDR1 mouse model. The success of each method was evaluated based on the quantity of calpain 3 produced across muscles.

What the results look like, each lane represents how much calpain 3 is in the sample, with a darker band indicating more protein:

From left to right, the samples are from the soleus muscle of an untreated LGMDR1 mouse, a normal/wild-type mouse, and an LGMDR1 mouse treated with our #3 therapy at 1e13 vg/kg.

RESULTS

Promoter	Slow Fibers	Fast Fibers	Heart
#2	✔✔	✔✔✔	
#3	✔✔✔	✔✔✔	
#7	✔✔		
#8	✔✔✔	✔	
#10			✔
#11	✔	✔	✔

✓ = some calpain 3, ✓✓ = moderate calpain 3, ✓✓✓ = abundant calpain 3

SIGNIFICANCE

First preclinical study for LGMDR1 that restores more than 100% of calpain 3 in fast and slow muscle fibers

and

does not require the addition of additional genetic elements (eg, microRNA) to prevent calpain 3 production in the heart.

FUTURE

We have identified a lead candidate for LGMDR1 gene therapy (#3). Before proceeding to the clinic, however, further validation and safety assessments are necessary.

We have shown that our gene therapy works at a low dose that would minimize an immune response to the treatment.

Functional studies are ongoing to confirm that restoration of the calpain 3 protein eases LGMDR1 symptoms.