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Gene therapy for Duchenne muscular dystrophy heart disease requires treating both heart and skeletal muscle

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Duchenne muscular dystrophy (DMD) is a lethal muscle wasting disease caused by mutations in the dystrophin gene. Affected children are wheelchair bound by the age of ten and die in their mid-twenties from respiratory and/or cardiac failure. Gene therapy represents a promising avenue for curing DMD. While significant progress has been made for treatment of skeletal muscle disease, few studies have investigated the potential of gene therapy to treat heart disease. A cure for DMD requires rescuing both skeletal and heart muscles. Gene therapy aims to deliver a functional copy of the dystrophin gene to affected muscle cells. However, the dystrophin gene is the largest gene in the body and cannot be effectively delivered with any currently available methods. This led researchers to develop abbreviated versions of the dystrophin gene. The most promising of these genes is a 7 kb mini-dystrophin gene which can completely restore skeletal muscle in the mdx mouse model of DMD. The potential of the mini-dystrophin gene for treating heart disease is uncertain. Cardiac specific mini-dystrophin gene expression improved but did not normalize heart function. To investigate whether the incomplete cardiac rescue is due to skeletal muscle disease, we generated double transgenic male mdx mice which expressed the mini-dystrophin gene in both heart and skeletal muscle. We performed comprehensive skeletal and cardiac muscle testing at 6 months of age. Restoration of skeletal muscle function was confirmed by the grip strength assay. Next, we performed an uphill treadmill assay to gauge overall cardiac performance. Double transgenic mice ran significantly farther than cardiac transgenic mice. Finally, we performed electrocardiographic (ECG) analysis to examine the function of the cardiac conduction system. ECG analysis revealed an improved heart rate for double transgenic mice when compared to heart-only transgenic mice. Taken together, these results support a role for skeletal muscle disease in modulating heart function. Furthermore, these findings highlight the importance of tailoring gene therapy approaches to treat both the heart and skeletal muscle.