

Mouse Model for Duchenne's Muscular Dystrophy

Duchenne's muscular dystrophy (DMD) is one of the most common lethal genetic diseases of childhood. DMD is an inherited X-linked disease that results in the loss of dystrophin, a protein involved in maintaining the integrity of muscle. C57BL/10ScSn-*Dmd*^{mdx}/J mice (common name *mdx*) have a loss-of-function mutation in the dystrophin gene that underlies progressive muscle degeneration starting about three weeks of age. The *mdx* mouse is the most published model of DMD (Grounds *et al.*, 2008). The objective of the study is to characterize muscle defects and histopathology in the *mdx* mice.

Study Design

- Male C57BL/10ScSn-*Dmd*^{mdx}/J (“*mdx*”; Stock Number 001801) and C57BL/10ScSnJ (“control”; Stock Number 000476) mice (N=6 for both)
- Mice subjected to grip strength testing at four and eight weeks of age
- Histopathology on muscle tissue (extensor digitorum longus, tibialis anterior, diaphragm, soleus) for signs of dystrophy at eight weeks of age

Deliverables

- 1 Histology blocks and slides of muscle tissue
- 2 Written report providing the following information:
 - a. Grip strength readings
 - b. Histological analysis of muscle fibers
 - c. Locomotor testing and blood/plasma collection upon request

Experimental Timeline

			Grip strength		Grip strength	Study Termination
Age (d)	21-24	25 - 27	28	29-55	56	
	Acclimation	Phenotyping				Necropsy

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Representative Data

Table 1: Reduced grip strength in the *mdx* mice. (N=6 per group)

Age (w)	Test	Group	Average Peak Tension (kg)	Standard Deviation	p Value
4	Forelimb	Control <i>mdx</i>	0.0674 0.0420	0.0080 0.0144	0.004
4	Hind limb	Control <i>mdx</i>	0.0327 0.0257	0.0040 0.0059	0.038
8	Forelimb	Control <i>mdx</i>	0.1205 0.0727	0.0216 0.0143	0.001
8	Hind limb	Control <i>mdx</i>	0.0639 0.0769	0.0193 0.0201	0.28

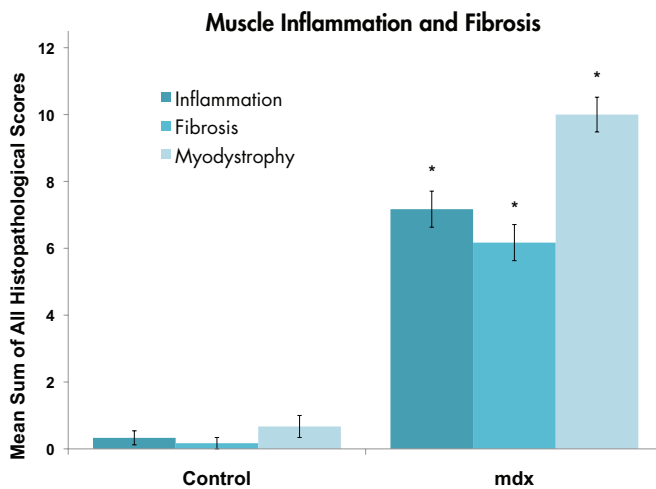


Figure 1. Increased inflammation and fibrosis in *mdx* muscle tissue. Muscle types listed in Study Design were dissected from control (N=6) and *mdx* (N=6) mice, sectioned, and scored for signs of inflammation, fibrosis and myodystrophy. Each muscle type was scored on a severity scale of zero to three. Sum values are reported with standard error. (*) $p = 0.0$ by Students T-test compared to control.

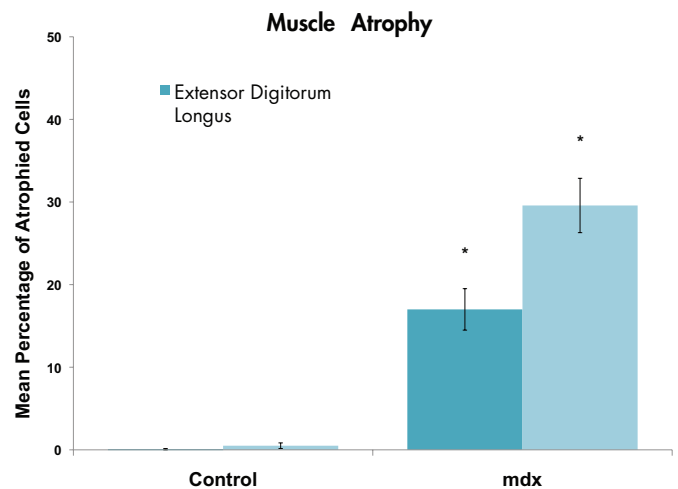


Figure 2. Increased atrophy in *mdx* muscle. Muscle fibers (N=200 per muscle type) were dissected from control (N=6) and *mdx* (N=6) mice and assessed for signs of atrophy. Values are reported as the mean with standard error. (*) $p = 0.0$ by Students T-test

Conclusions

- The *mdx* mice show reduced grip strength (both forelimb and hind limb) at four weeks of age compared with control mice. At eight weeks, the *mdx* forelimb strength decreases while the hind limbs show normal strength. Such findings reflect the progression of the acute phase of muscle necrosis in the young *mdx* mice (Grounds *et al.*, 2008).
- Muscle atrophy, inflammation and fibrosis are present in the *mdx* mice at eight weeks of age.

References

Grounds MD, *et al.* 2008. Towards developing standard operating procedures for pre-clinical testing in the *mdx* mouse model of Duchenne muscular dystrophy. *Neurobiol Dis* 31:1-19.

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