Sexually dimorphic skeletal muscle and cardiac dysfunction in a mouse model of limb girdle muscular dystrophy 2i.

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Abstract
The fukutin-related protein P448L mutant mouse replicates many pathologies common to limb girdle muscular dystrophy 2i (LGMD2i) and is a potentially strong candidate for relevant drug screening studies. Because striated muscle function remains relatively uncharacterized in this mouse, we sought to identify metabolic, functional and histological metrics of exercise and cardiac performance. This was accomplished by quantifying voluntary exercise on running wheels, forced exercise on respiratory treadmills and cardiac output with echocardiography and isoproterenol stress tests. Voluntary exercise revealed few differences between wild-type and P448L mice. By contrast, peak oxygen consumption (VO₂peak) was either lower in P448L mice or reduced with repeated low intensity treadmill exercise while it increased in wild-type mice. P448L mice fatigued quicker and ran shorter distances while expending 2-fold more calories/meter. They also received over 6-fold more motivational shocks with repeated exercise. Differences in VO₂peak and resting metabolic rate were consistent with left ventricle dysfunction, which often develops in human LGMD2i patients and was more evident in female P448L mice, as indicated by lower fractional shortening and ejection fraction values and higher left ventricle systolic volumes. Several traditional markers of dystrophinopathies were expressed in P448L mice and were exacerbated by exercise, some in a muscle-dependent manner. These include elevated serum creatine kinase and muscle central nucleation, smaller muscle fiber cross-sectional area and more striated muscle fibrosis. These studies together identified several markers of disease pathology that are shared between P448L mice and human subjects with LGMD2i. They also identified novel metrics of exercise and cardiac performance that could prove invaluable in preclinical drug trials. NEW & NOTEWORTHY Limb-girdle muscular dystrophy 2i is a rare dystroglycanopathy that until recently lacked an appropriate animal model. Studies with the FKRP P448L mutant mouse began assessing muscle structure and function as well as running gait. Our studies further characterize systemic muscle function using exercise and cardiac performance. They identified many markers of respiratory, cardiac and skeletal muscle function that could prove invaluable to better understanding the disease and more importantly, to preclinical drug trials.

KEYWORDS: LGMD2i; exercise; heart; muscle; muscular dystrophy

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