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 pathologies common to limb-girdle muscular dystrophy 2i (LGMD2i) and is a 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 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 (VO_2peak) was 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 6-fold more motivational shocks with repeated exercise. Differences in VO_2peak 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.


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