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Sensorimotor skills in *Fxn* KO/*Mck* mutants deficient for frataxin in muscle

Mohammed Filali[a,*], *Robert Lalonde*[b], *Catherine Gérard*[a], *Zoé Coulombe*[a], *Jacques P. Tremblay*[a]

[a]*Plateforme d'analyse fonctionnelle du comportement animal, Axe Neurosciences, Centre Hospitalier Universitaire de Québec, Département de Médecine Moléculaire, Faculté de Médecine Université Laval, Canada*

[b]*Université de Rouen, Faculté de Sciences and Département de Psychologie, Laboratoire ICONES EA 4699, 76821 Mont-Saint-Aignan, France*

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ABSTRACT

Friedreich ataxia is the most common autosomal recessive disorder of the cerebellum, causing degeneration of spinal sensory neurons and spinocerebellar tracts. The disease is caused by severely reduced levels of frataxin, a mitochondrial protein involved in iron metabolism. An experimental model has been generated by crossing mice homozygous for a conditional allele of the *Fxn* gene with mice heterozygous for a deleted exon 4 of *Fxn* carrying a tissue-specific Cre transgene under control of the muscle creatine kinase promoter. Relative to wild-type, *Fxn* null mutants were impaired on tests of motor coordination comprising horizontal bar, vertical pole, and the rotorod as well as displaying gait anomalies and the hindlimb clasping response. The *Fxn* KO/*Mck* model reproduces some key features of patients with Friedreich ataxia and provides an opportunity of ameliorating their symptoms with experimental therapies.

1. Introduction

Patients with Friedreich ataxia are characterized by degenerating cerebellar neurons and spinocerebellar tracts along with peripheral sensory nerves associated with their dorsal and cranial root ganglia (Koeppen and Mazurkiewicz, 2013; Ribaï et al., 2007). The disease is caused by a GAA polyglutamate triplet expansion, decreasing transcription of the *FXN* gene encoding frataxin (Campuzano et al., 1996, 1997; Dürr et al., 1996), a protein involved in iron function (Babcock et al., 1997; Delatycki et al., 1999; Stemmler et al., 2010). In the terminal stage, the patients often display Cheyne–Stokes breathing from bulbar damage (Lalonde and Botez, 1991) and often die from cardiac anomalies (Tsou et al., 2011).

Frataxin levels in the nervous system of the normal mouse are maximal at the level of the spinal cord, particularly dorsal root ganglia (Jiralerspong et al., 1997), site of the most severe damage occuring in Friedreich ataxia. As expected from genetic analyses, inactivation of *Fxn* in the mouse leads to anomalies in neural and cardiac tissues (Cossée et al., 2000; Puccio et al., 2001). A null deletion of *Fxn* in all murine tissues causes embryonic lethality (Cossée et al., 2000). Subsequently,

*Correspondence to: CHUQ-CHUL Research Center, 2705 Blvd Laurier, Local T-2-50, Québec, Québec, Canada G1V 4G2. Fax: +1 418 654 2761.
E-mail address: mohammed.filali@crchul.ulaval.ca (M. Filali).

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two conditional knockout (KO) models were generated without embryonic lethality but with shorter life-spans than normal, one using neuron-specific enolase (*Fxn* KO/*Nse*) as the promoter and the other muscle-specific creatinine kinase (*Fxn* KO/*Mck*) (Puccio et al., 2001). Accordingly, the models mimic two facets of the disease, one regarding the consequence of frataxin deficiency in brain and the other in muscle. In the present study, *Fxn* KO/*Mck* mice deficient for frataxin in skeletal and cardiac muscle were selected for behavioral analyses. Unlike the *Fxn* KO/*Nse* model displaying dystonia and crawling, *Fxn* KO/*Mck* mice are not overtly distinguishable from controls on casual inspection in their home-cage.

Fxn KO/*Mck* mice have an average life-span of approximately 4 months, reduced body weight, and cardiac hypertrophy, possibly as a result of iron accumulation in mitochondrial fractions of heart muscle (Puccio et al., 2001). *Fxn* KO/*Mck* mice were evaluated on measures directly relevant to the disease, including motor activity and coordination. Motor activity was recorded in the open-field. Motor coordination tests included a horizontal bar, a vertical pole, and a rotorod (Carter et al., 2001; Crawley, 2008; Lalonde and Strazielle, 2013). In addition, footprint assays sensitive to a mouse model of ataxia telangiectasia (Barlow et al., 1996) and reflecting the extent of muscle loosening was used, together with hindlimb clasping, common to many murine mutations (Lalonde and Strazielle, 2011) as well as the hot-plate response of pain thresholds (Hunskaar et al., 1986), the latter used as a control test since Friedreich ataxia mostly involves decreased somatosensory responses of the lemniscal system (Koeppen and Mazurkiewicz, 2013; Ribaï et al., 2007).

2. Results

2.1. Motor activity

Fxn KO/*Mck* mice did not differ from controls on any measure of motor activity (Fig. 1), including distance traveled ($t_{29}=1.56$, $P>0.05$), immobility time ($t_{29}=1.58$, $P>0.05$), rears ($t_{29}=0.16$, $P>0.05$), or rearing duration ($t_{29}=1.16$, $P>0.05$).

2.2. Hindpaw clasping and body weight

Hindpaw clasping in *Fxn* KO/*Mck* mice was of longer duration than controls ($t_{29}=2.2$, $P<0.05$) (Fig. 2). In contrast, there was no intergroup difference in body weight ($t_{29}=0.01$, $P>0.05$) (Fig. 2).

2.3. Motor coordination and footprint patterns

As indicated in Fig. 3, *Fxn* KO/*Mck* mice fell from the horizontal bar sooner than controls ($t_{29}=2.09$, $P<0.05$) and took a longer time before righting ($t_{29}=3.7$, $P<0.0001$). Likewise, *Fxn* KO/*Mck* mice took a longer time before climbing up ($t_{29}=4.17$, $P<0.001$) or down ($t_{29}=3.72$, $P<0.001$) from the vertical pole (Fig. 4). When allowed to run down an alley, stride length was decreased in *Fxn* KO/*Mck* mice relative to controls ($t_{29}=3.84$, $P<0.01$) and hindbase width was increased ($t_{29}=3.1$, $P<0.05$) (Fig. 5). As with the previous tests of motor skills, *Fxn* KO/*Mck* mice fell sooner than controls from the revolving beam ($t_{29}=2.22$, $P<0.05$) (Fig. 6).

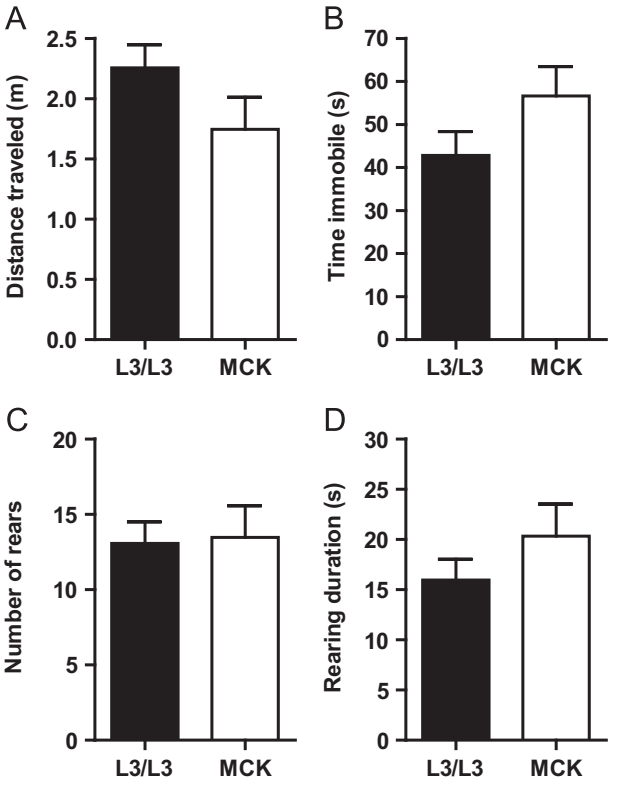

Fig. 1 – Home-cage activity in *Fxn* KO/MCK mice and controls.

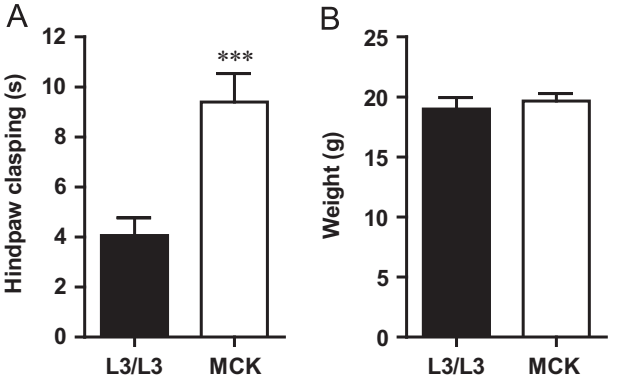

Fig. 2 – Hindpaw clasping and body weight in *Fxn* KO/MCK mice and controls.

2.4. Hot-plate

In contrast to the motor coordination tests, there was no intergroup difference in the hot-plate test for withdrawal behaviors ($t_{29}=0.08$, $P>0.05$) (Fig. 6).

3. Discussion

Fxn KO/*Mck* mice are characterized by a shorter life-span than controls, possibly caused by cardiac hypertrophy (Puccio