A Novel G1528C Knock-in model of LCHAD deficiency recapitulates aspects of the human clinical phenotype

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Background

Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) is a disorder of fatty acid oxidation caused by a common DNA point mutation, G1528C, in the HADHA gene which leads to a amino acid substitution, E510Q, in the alpha subunit of trifunctional protein (TPFs). Patients with LCHADD develop chorioretinopathy and peripheral neuropathy not observed in the other fatty acid oxidation disorders (FAODs) in addition to symptoms such as hypoglycemia and cardiomyopathy. Previous HADHA knock-out mouse models have suffered from neonatal lethality. Here we report a new CRISPR/Cas9 knock-in model of G1528C that recapitulates aspects of the human phenotype.

Model Creation

Using CRISPR/Cas9 with homologous recombination, c.1528G>C mutation and a silent mutation (to prevent further CRISPR cuts) was introduced into HADHA of a C57BL/6j mouse

Mouse and human TFPs proteins are highly conserved. The mouse G1528C knock-in introduces a mutation, p.S10E>Q, homologous to the human common LCHADD mutation

Phenotyping of Homozygotes

General FAQ

LCHADD mice show reduced viability

Cardiac tissue expresses TFPs but oxidizes less palmitate than WT

LCHADD mice accumulate serum 3-hydroxyacylcarnitines and oxidize less fat as shown by higher Respiratory exchange quotient (RER)

LCHADD mice show lower fasting glucose and quicker exercise exhaustion times

Discussion

Phenotyping of the model demonstrated evidence of cardiac, fasting and exercise intolerance phenotypes similar to other mouse models of FAODs while also demonstrating LCHADD-specific retinal and neurological abnormalities. The G1528C mutant mouse is a promising model for future research into LCHADD. This G1528C knock-in mouse is the first reported viable model of LCHADD.

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