B6-Chr1^{YP1}-Speg 3mutations

Strain Name: C57BL/6JGpt-Chr1^{YP1}Speg$^{em1Cin(S2461A\&S2462A\&T2463A)}$/Gpt
Strain Type: Point mutation
Strain Number: T057251
Background: C57BL/6JGpt-Chr1^{YP1}/Gpt

Description

Striated muscle preferentially expressed protein kinase (SPEG) is a serine/threonine kinase, a member of the myosin light chain kinase family, that plays an important role in regulating cardiac Ca^{2+} uptake. It has been found that *SPEG* mutations in humans lead to central nuclear myopathy and dilated cardiomyopathy[1]. Further studies have shown that SPEG phosphorylates sarcoplasmic/endoplasmic reticulum calcium ATPase 2a (SERCA2a), which regulates Ca^{2+} uptake in cardiomyocytes[2]. However, when Ser 2461, Ser 2462, and Thr 2463 are replaced by non-phosphorylatable alanines, this results in the inability of SPEG to phosphorylate SERCA2a, resulting in impaired Ca^{2+} uptake in cardiomyocytes as well as impaired cardiac function[3].

The background mouse for B6-Chr1^{YP1}-Speg 3mutations is B6-Chr1^{YP1} (strain no. D000750), which is a wild-sourced chromosome 1 replacement line mouse with C57BL/6JGpt as the receptor, with metabolic abnormalities such as spontaneous obesity and spontaneous fatty liver phenotype. The T057251 strain developed by GemPharmatech has the *Speg S2461A&S2462A&T2463A* mutations in the background of B6-Chr1^{YP1}, which provides a new genetically engineered mouse model for the study of the mechanism of this mutation site.

Strategy

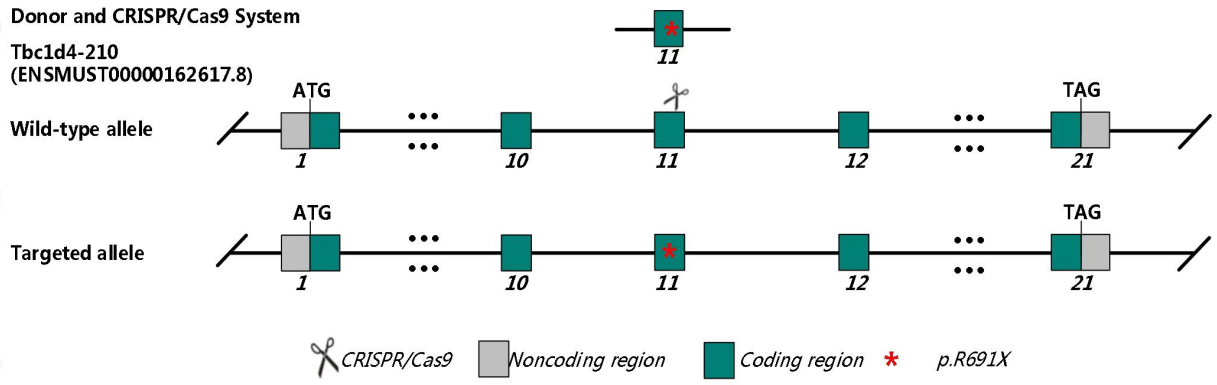

Fig.1 Schematic diagram of B6-Chr1^{YP1}-Speg 3mutations model stratery.

Application

1. Study on the signaling mechanisms of SPEG-related pathways
2. Study on the the relevant role and mechanism of SPEG in diabetic cardiomyopathy

Data support

1. Detection of mouse *Speg* mRNA level

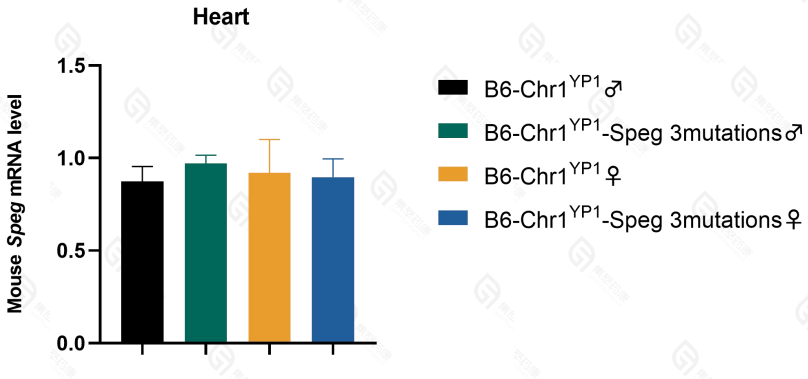

Fig 2. The mRNA expression of mouse *Speg* in B6-Chr1^{YP1}-Speg 3mutations.

The mRNA expression of mouse Speg in the mice model were detected by RT-qPCR using primer specific to mouse *Speg*. (n=3♂, 3♀)

2. Identification of S2461A&S2462A&T2463A mutations of *Speg*

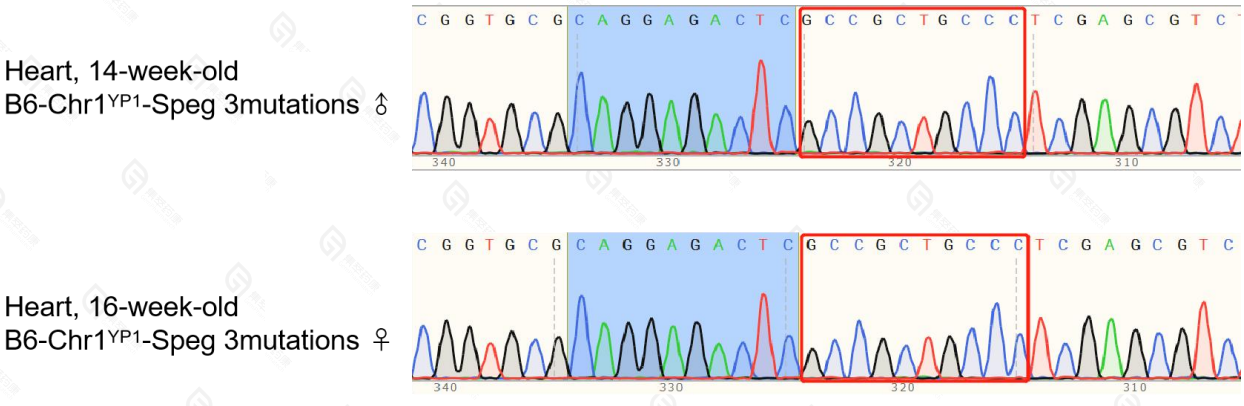

Fig 3. The mutations of S2461A&S2462A&T2463A were positive in the strain of B6-Chr1^{YP1}-Speg 3mutations.

The target fragment including S2461A&S2462A&T2463A mutations site was obtained by RT-PCR, and then high-throughput sequencing was employed to identify S2461A&S2462A&T2463A mutation sites in the heart tissue of the B6-Chr1^{YP1}-Speg 3mutations mice. (n=1♂, 1♀)

Reference

1. Agrawal PB, Pierson CR, Joshi M, et al. SPEG interacts with myotubularin, and its deficiency causes centronuclear myopathy with dilated cardiomyopathy. Am J Hum Genet. 2014 Aug 7;95(2):218-26.
2. Quan C, Li M, Du Q, et al. SPEG Controls Calcium Reuptake Into the Sarcoplasmic Reticulum Through Regulating SERCA2a by Its Second Kinase-Domain. Circ Res. 2019 Mar;124(5):712-726.
3. Quan C, Du Q, Li M, et al. A PKB-SPEG signaling nexus links insulin resistance with diabetic cardiomyopathy by regulating calcium homeostasis. Nat Commun. 2020 May 4;11(1):2186.