B6-*Casr*-L723Q

Strain Name: B6/JGpt-*Casr*$^{em1Cin(L723Q)}$/Gpt
Strain Type: Knock-in
Strain ID: T054637
Background: C57BL/6JGpt

Description

The calcium-sensing receptor, also known as CASR or GPRC2A, is a cell surface receptor that belongs to the family of G-protein coupled receptors. CASR is involved in sensing calcium fluctuations in the extracellular matrix of cells and plays an important role in calcium homeostasis and parathyroid hormone secretion. CASR is highly expressed in parathyroid glands, and its expression is precisely regulated by the secretion of parathyroid hormone (PTH) through the reabsorption of Ca^{2+} from bone, urinary system, and intestine. Abnormal expression levels and receptor activities of CASR will cause many diseases, such as familial hypocalciuric hypercalcemia type1 (FHH1), neonatal severe hyperparathyroidism (NSHPT), autosomal dominant hypocalcemia type 1 (ADH1), and asthma[1-2].

Studies demonstrated that the germline gain-of-function mutation of CASR caused ADH1. CASR signal via multiple pathways, including intracellular calcium mobilization and the ERK arm of the MAPK cascade to regulate PTH secretion and urinary calcium excretion. ADH1 is characterized by hypocalcemia, increased circulating phosphate concentrations, and a relative hypercalciuria with urinary calcium-to-creatinine ratios that are within or above the reference range. Application of Calcilytics (antagonists of CASR) may be potentially developed into targeted therapy for ADH1[3-4].

*Nuf m*ice, which develop hypocalcemia in association with a gain-of-function CASR mutation, Leu723Gln, have become a preferred model for ADH1 study as well as preclinical therapy evaluation[4]. B6-*Casr*-L723Q strain is created in the C57BL/6JGpt background (strain number T054637) in Gempharmatech based on the mutant type of *Nuf m*ice, Leu723Gln. B6-*Casr*-L723Q strain exhibited similar phenotype to *Nuf* mice, with hypocalcemia and hyperphosphatemia. Therefore, B6-*Casr*-L723Q strain is an ideal model for preclinical anti-ADH1 drug evaluation.

The B6-*Casr*-L723Q strain was created at GemPharmatech using gene editing technology whereby a point mutation was introduced in exon 7, leading to Leu723Gln point mutation of CASR protein.

Strategy

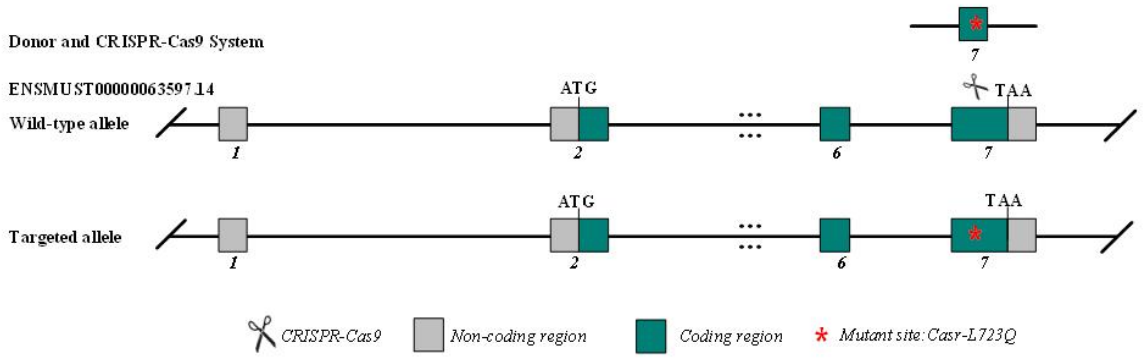

Fig 1. The B6-*Casr*-L723Q strain strategy

A single point mutation was introduced into exon 7 of *Casr* gene via CRISPR/Cas9 based gene editing.

Applications

1.Anti-autosomal dominant hypocalcemia type1 (ADH1) drug screening and efficacy test.

2.Research on related diseases (such as hypocalcemia and hyperphosphatemia) caused by defects of *Casr* (L723Q point mutation).

Data support

1. Blood biochemistry analysis

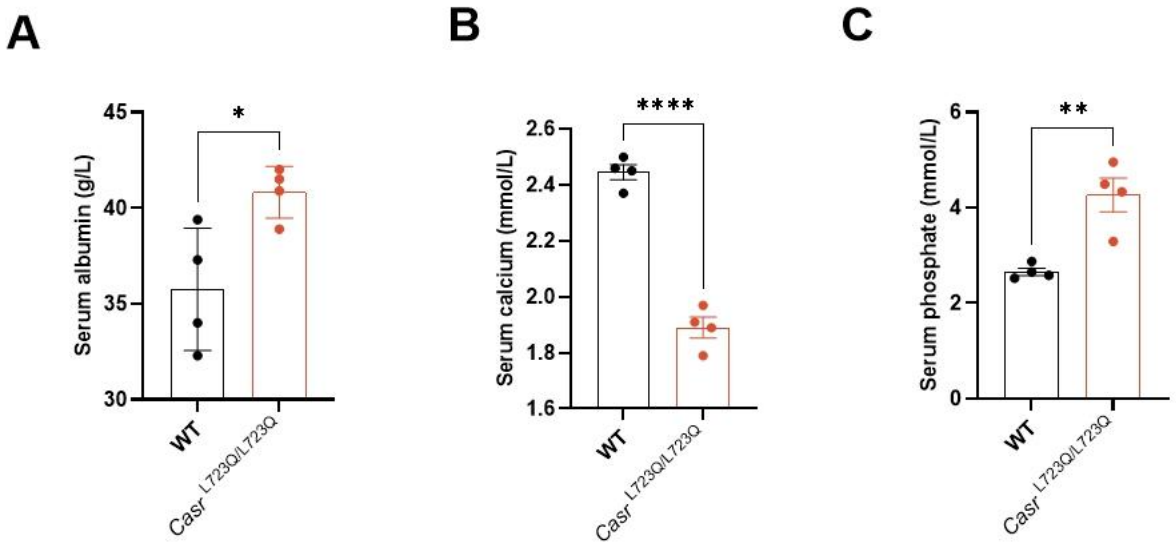

Fig 2. Analysis of clinical-relevant biochemistry parameters

Blood from male WT (C57BL/6J) mice (n=4) and *Casr*$^{L723Q/L723Q}$ (B6-*Casr*-L723Q homozygous) mice (n=4) were collected and analyzed for serum ALB (A), calcium (B) and phosphate (C) level. These results demonstrated that *Casr*$^{L723Q/L723Q}$ mice displayed hypocalcemia and hyperphosphatemia. All data represent as MEAN ± SEM. Comparison between groups involved unpaired two-tailed Student's t test, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

References

1. Wen T, et al. "Structural basis for activation and allosteric modulation of full-length calcium-sensing receptor". Sci Adv 7.23 (2021): eabg1483.
2. Sundararaman SS, van der Vorst EPC. "Calcium-Sensing Receptor (CaSR), Its Impact on Inflammation and the Consequences on Cardiovascular Health". Int J Mol Sci 22.5 (2021): 2478.
3. Hannan FM, et al. "The Calcilytic Agent NPS 2143 Rectifies Hypocalcemia in a Mouse Model with an Activating Calcium-Sensing Receptor (CaSR) Mutation: Relevance to Autosomal Dominant Hypocalcemia Type 1 (ADH1)." Endocrinology 156.9 (2015): 3114-3121.
4. Hannan FM, et al. "Calcilytic NPSP795 Increases Plasma Calcium and PTH in an Autosomal Dominant Hypocalcemia Type 1 Mouse Model". JBMR Plus 4.10 (2020): e10402.