B6-Gpbar1-p.H88Y

Strain Name: C57BL/6JGpt-*Gpbar1*$^{em1Cin(p.H88Y)}$/Gpt
Strain Type: Knock-in
Strain Number: T055015
Background: C57BL/6JGpt

Description

G protein-coupled bile acid receptor 1 (Gpbar1), which also known as TGR5, is a member of the GPCRs subfamily. As a receptor for bile acids (BAs), it can be activated after binding with BAs [1]. Regulation of glucose metabolism targeting Gpbar1 plays an important role in diabetes.

Gpbar1 induced metabolic alterations by binding with BAs[2]. It has been reported that Gpbar1 plays an important role in intestinal regulation by regulating downstream signaling pathways. Gpbar1 activates type 2 deiodinase upon binding with BAs, which then activates thyroid hormones in brown adipose tissue (BAT) and muscle tissue[3]. Gpbar1 signaling has also been reported to improve liver and pancreas function and increase glucose tolerance in obese mice by inducing the release of intestinal glucagon-like peptide-1 (GLP-1). Recently, Gpbar1 has been found to have species differences. Studies have showed that amino acid H88 in mGpbar1 (Y89 in hGpbar1) is the key amino acid that causes species differences[4] between human and mice, thus affecting the effect of Gpbar1 agonists.

Gempharmatech used CRISPR/Cas9 system to introduce Gpbar1-H88Y mutation into mice, and successfully constructed the Gpbar1 gene H88Y mutation model B6-Gpbar1-p.H88Y (T055015). B6-Gpbar1-p.H88Y can be used to evaluate the efficacy of clinical drugs targeting Gpbar1 for the treatment of diabetes.

Strategy

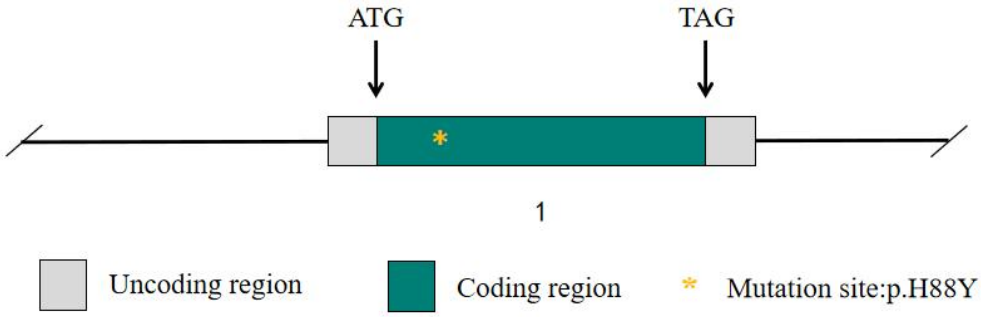


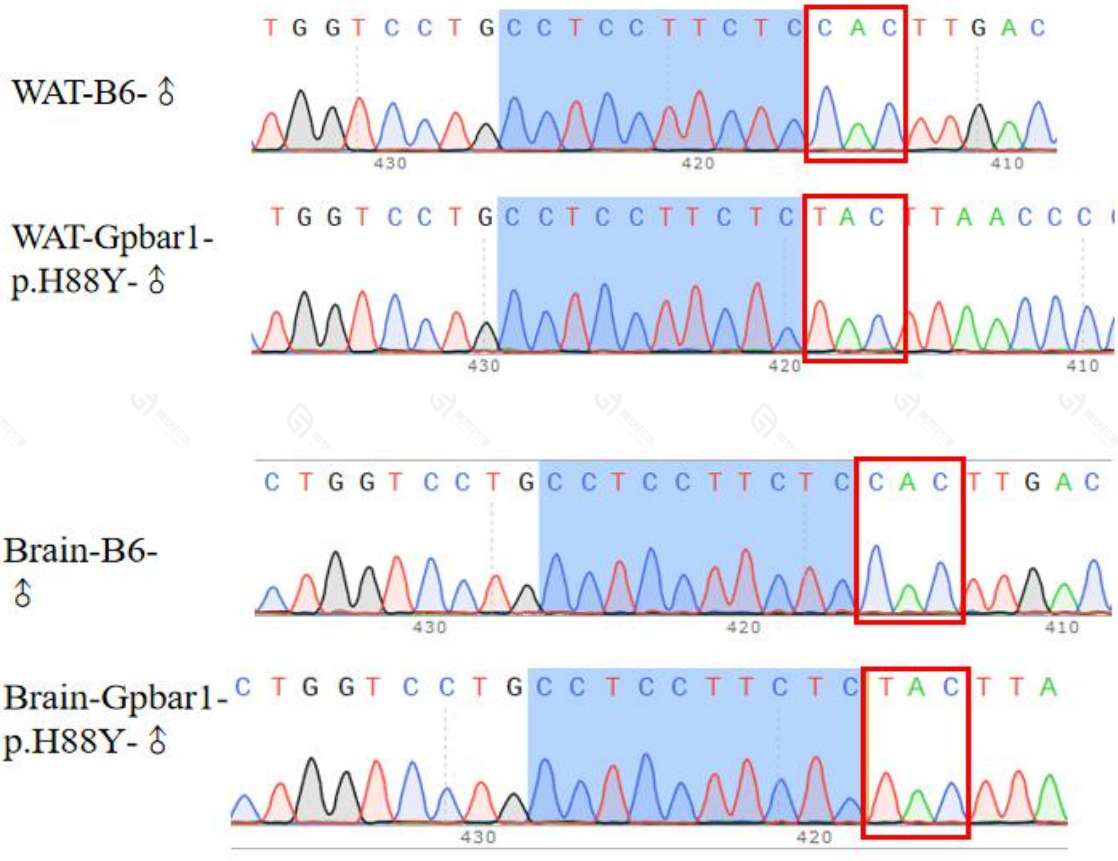
Fig.1 Schematic diagram of B6-Gpbar1-p.H88Y model strategy.

Applications

1. Screening and efficacy evaluation of drugs related to human diabetes
2. The mechanisms targeting Gpbar1 in diabetes

Data support

1. Gpbar1 p. H88y point mutation detection



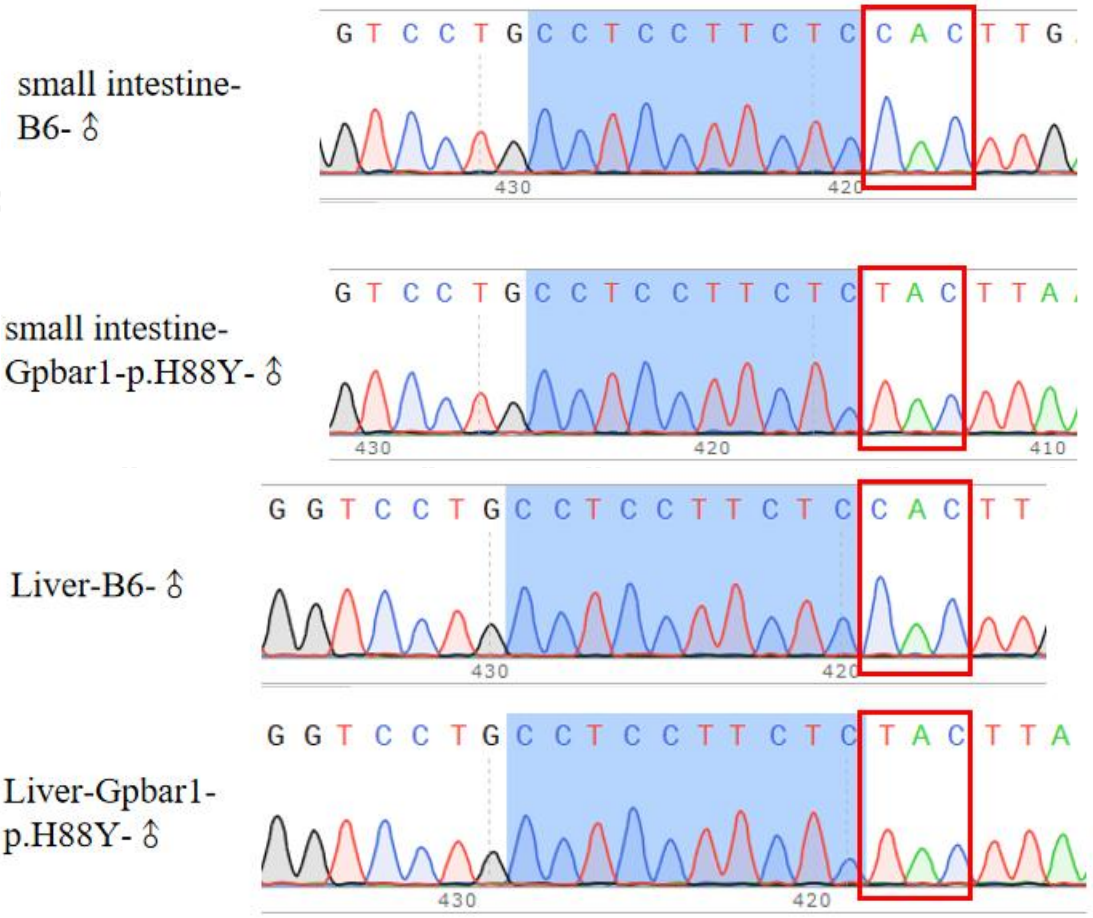
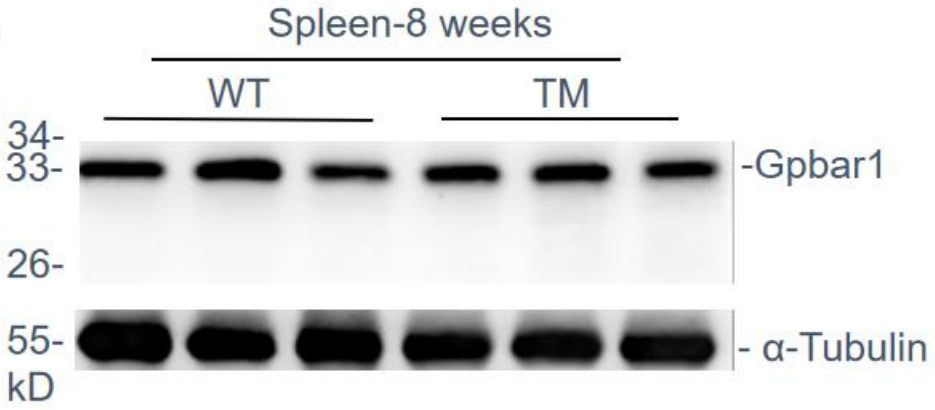


Fig 2. Gpbar1-H88Y mice were positive, B6 mice were negative for Gpbar1 point mutation
The white fat, brain, small intestine and liver tissues from B6 mice and Gpbar1-H88Y mice were detected by RT-PCR. The fragment containing the H88Y mutation site was amplified specifically, and amplified fragments were detected by high-throughput sequencing.The B6 group was male B6 background mice, and Gpbar1-p. H88Y was male point mutation mice.

2. Detection of Gpbar1 protein expression



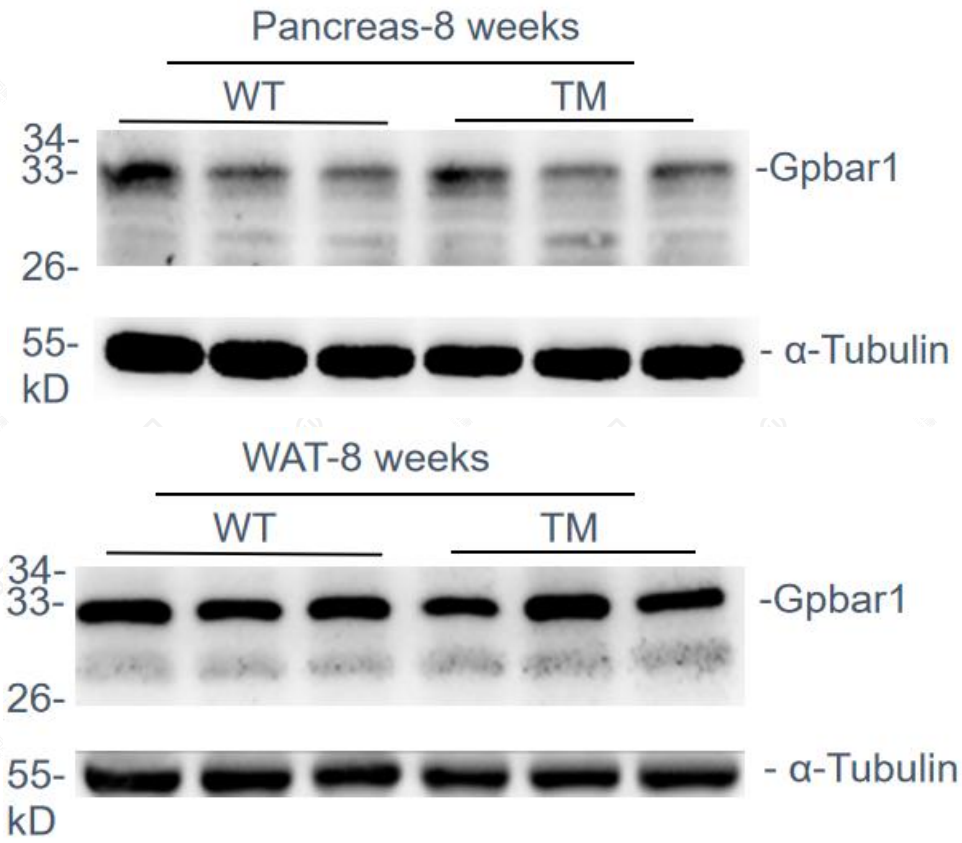


Figure 3 Gpbar1 protein was successfully expressed in B6-Gpbar1-p.H88Y mice

The spleen, pancreas and fat tissues of B6 mice and Gpbar1- p.H88Y mice were detected by Western blot used an antibody recognized mouse Gpbar1. The WT group consisted of three male B6 mice. The TM group consisted of three male Gpbar1-p.H88Y mice.

References

1. Wang XX, Xie C, Libby AE, et al. The role of FXR and TGR5 in reversing and preventing progression of Western diet-induced hepatic steatosis, inflammation, and fibrosis in mice. J Biol Chem. 2022;298(11):102530.

2. Thomas C, Gioiello A, Noriega L, et al. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab. 2009;10(3):167-177.

3. Watanabe, M., Houten, S.M., Mataki, C., Christoffolete, M.A., Kim, B.W., Sato, H., Messaddeq, N., Harney, J.W., Ezaki, O., Kodama, T., et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. Nature 439, 484–489.

4. Yun Y, Zhang C, Guo S, et al. Identification of Betulinic Acid Derivatives as Potent TGR5 Agonists with Antidiabetic Effects via Humanized TGR5H88Y Mutant Mice. J Med Chem. 2021;64(16):12181-12199.