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Novel frame-shift mutation in *Slc5a2* encoding SGLT2 in a strain of senescence-accelerated mouse SAMP10

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ABSTRACT

The senescence-accelerated mouse prone10 (SAMP10) strain, a model of aging, exhibits cognitive impairments and cerebral atrophy. We noticed that SAMP10/TaSlc mice, a SAMP10 substrain, have developed persistent glucosuria over the past few years. In the present study, we characterized SAMP10/TaSlc mice and further identified a spontaneous mutation in the *Slc5a2* gene encoding sodium-glucose co-transporter (SGLT) 2. The mean concentration of urine glucose was high in SAMP10/TaSlc mice and increased further with advancing age, whereas other strains of senescence-accelerated mice, including SAMP1/SkuSlc, SAMP6/TaSlc and SAMP8/TaSlc or normal aging control SAMR1/TaSlc mice, exhibited no detectable glucose in urine. SAMP10/TaSlc mice consumed increasing amounts of food and water compared to SAMR1/TaSlc mice, suggesting the compensation of polyuria and the loss of glucose. Oral glucose tolerance tests showed decreased glucose reabsorption in the kidney of SAMP10/TaSlc mice. In addition, blood glucose levels decreased in an age-dependent fashion. The kidney was innately larger than that of control mice with no histological alterations. We examined the expression levels of glucose transporters in the kidney. Among SGLT1, SGLT2, glucose transporter (GLUT) 1 and GLUT2, we found a significant decrease only in the level of SGLT2. DNA sequencing of SGLT2 in SAMP10/TaSlc mice revealed a single nucleotide deletion of guanine at 1236, which resulted in a frameshift mutation that produced a truncated protein. We designate this strain as SAMP10/TaSlc-*Slc5a2*^{slc} (SAMP10-ΔSglt2). Recently, SGLT2 inhibitors have been demonstrated to be effective for the treatment of patients with type 2 diabetes (T2D). SAMP10-ΔSglt2 mice may serve as a unique preclinical model to study the link between aging-related neurodegenerative disorders and T2D.

1. Introduction

Senescence-accelerated mice (SAMs) were developed by a group at Kyoto University in Japan [1]. Cross-breeding of AKR/J with a few other strains resulted in several mouse lines with different characteristics. Inbred senescence-prone (SAMP) strains as models of accelerated senescence and senescence-resistant (SAMR) strains as the normal aging control were reported in 1981 [2]. Subsequent studies demonstrated aging-related phenotypes in these mice [3,4]. By 1992, substrains of SAMP mice had been established in Kyoto University based on pathological phenotypes such as amyloidosis and immune system deficiency (SAMP1) [5,6], osteoporosis (SAMP6) [7], accelerated deficits in learning and memory (SAMP8) [8], and deficits in learning and memory with brain atrophy (SAMP10) [9].

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Thereafter, by 2002, these strains were re-established under specific pathogen-free (SPF) conditions in Japan SLC (Hamamatsu-city, Shizuoka, Japan) as SAMP1/SkuSlc, SAMP6/TaSlc, SAMP8/TaSlc, SAMP10/TaSlc and SAMR1/TaSlc [1,10]. On the other hand, the SAMP10/Ta strain has been maintained at the Institute for Developmental Research, Aichi Human Service Center since 1998 and was renamed as SAMP10/TaIdr. Therefore, SAMP10/TaSlc and SAMP10/TaIdr have been bred independently but are derived from the same SAMP10 strain. Both strains of SAMP10 mice show age-related brain atrophy, lowered learning and memory abilities and depressive behavior [11]. In the brains of SAMP10/TaIdr mice, it has been suggested that neuronal DNA damage [12], loss of synapse [13], impairment of proteasome activity [14], and microglial impairment [15] are involved in age-related neurodegeneration. We have demonstrated additional characteristics in SAMP10/TaSlc, including increased superoxide generation [16], DNA oxidative damage [17], and a decrease in glutathione peroxidase [18], and have reported preventive effects of antioxidative agents such as green tea catechin and β-cryptoxanthin on neurodegeneration in these mice [19–21].

In the present study, we report that SAMP10/TaSlc exhibits persistent glucosuria and lowered expression of *Slc5a2*. Based on DNA sequencing, we identified a nucleotide deletion in the *Slc5a2* gene of SAMP10/TaSlc. In contrast, we found that SAMP10/TaIdr mice developed no glucosuria and exhibited no mutation in the *Slc5a2* gene. These results indicate that the mutation in the *Slc5a2* gene occurred spontaneously in SAMP10/TaSlc. As the *Slc5a2* gene encodes the sodium-glucose co-transporter SGLT2, we designated this strain as SAMP10/TaSlc-*Slc5a2*^{slc} (SAMP10-ΔSglt2).

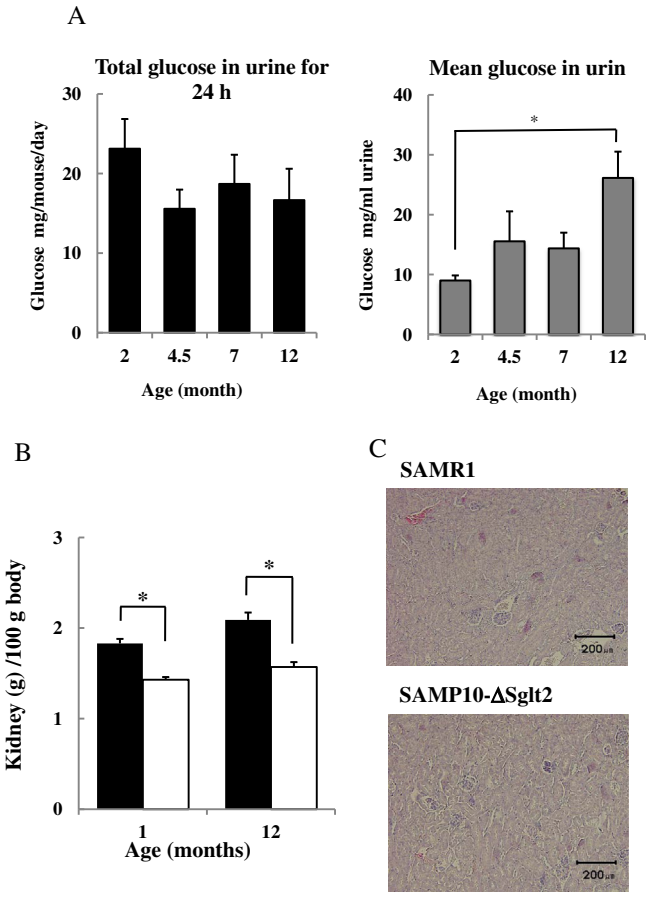

Fig. 1. Urinal glucose excretion and hypertrophy of kidney in SAMP10-ΔSglt2 mice. (A) SAMP10-ΔSglt2 mice (2–12 months of age) fasted for 24 h were given glucose (2 g/kg body weight) orally. Total glucose amounts in urine were measured for 24 h and mean glucose levels were compared (n = 3–8). (B) Kidney weight (g/100 g weight) of SAMP10-ΔSglt2 (closed column) was compared to SAMR1 (open column) at 1 and 12 months of age (n = 10–21, $^{*}p < 0.002$). (C) Kidney sections of 1-month-old SAMR1 and SAMP10-ΔSglt2 were stained with hematoxylin–eosin.

2. Materials and methods

2.1. Animals

Male SAMP10/TaSlc mice were purchased from Japan SLC (Hamamatsu-city, Shizuoka, Japan) and bred under conventional conditions in a temperature- and humidity-controlled room with a 12-h light/dark cycle (light period, 08.00–20.00 h; temperature, 23 ± 1 °C; relative humidity, 55 ± 5%). Experimental mice had free access to a normal diet (CE-2; Clea Co. Ltd., Tokyo, Japan) and water. Male SAMR1/TaSlc (SAMR1) mice, which have normal longevity and a very similar genetic background to SAMP10/TaSlc mice, were used as control mice. All experimental protocols were approved by the University of Shizuoka Laboratory Animal Care Advisory Committee and were in accordance with the guidelines of the US National Institutes of Health for the care and use of laboratory animals.

2.2. Measurement of glucose in urine and preparation of kidney tissue sections

Diagnosis chips were used to check glucosuria (Pretest 5bII, Wako, Wako Pure Chemicals Industries, Ltd., Osaka, Japan). Mice were fasted for 24 h. After glucose (2 g/kg body weight) was administered orally, each mouse was housed singly in a metabolic cage for 24 h with free access to water but without feeding. Urine was collected for 24 h. The total volume of urine was recorded and the concentration of glucose in urine was measured using a glucose assay kit (Glucose CII Test, Wako). Kidney specimens fixed with 10% formaldehyde in phosphate buffer were embedded in paraffin. Sections of 5 μm in thickness were stained with hematoxylin–eosin.

2.3. Diurnal glucose levels in serum and oral glucose tolerant test (OGTT)

Diurnal levels of blood glucose were observed for 24 h with free access to food and water. Blood glucose levels were measured every 3 h using a blood glucose meter and test tips (Terumo Corp. Japan, Tokyo, Japan). For OGTT, mice were fasted for 24 h. After glucose was administered orally (2 g/kg), blood glucose levels were measured for 2 h.

2.4. Glucose transporters in the kidney

Total RNA was extracted from the kidney using Trizol reagent (Invitrogen, Tokyo, Japan). cDNA samples were amplified according to the manufacturer's protocol using a kit (Ready To-Go You-Prime First strand beads, GE Healthcare Japan, Tokyo, Japan). The expression levels of SGLT1, SGLT2, GLUT1 and GLUT2 were measured using reverse-transcription polymerase chain reaction (RT-PCR). The following PCR cycles were used: initial denaturation at 95 °C for 5 min, followed by 20–25 cycles at 95 °C for 1 min, 58 °C for 1 min, and 72 °C for 1 min. PCR products were electrophoresed on a 1.2% (w/v) agarose gel (Bio-Rad Laboratories, Hercules, CA) containing ethidium bromide and visualized under UV illumination. RT-PCR products were measured using Scion Image analysis software. The amplified SGLT2 cDNA was used for sequencing.

The following primers were used in the study: SGLT2 forward 5′-AGG ATC CAT CTG TGG CA-3′, reverse 5′-ACG GGG CAC AAA

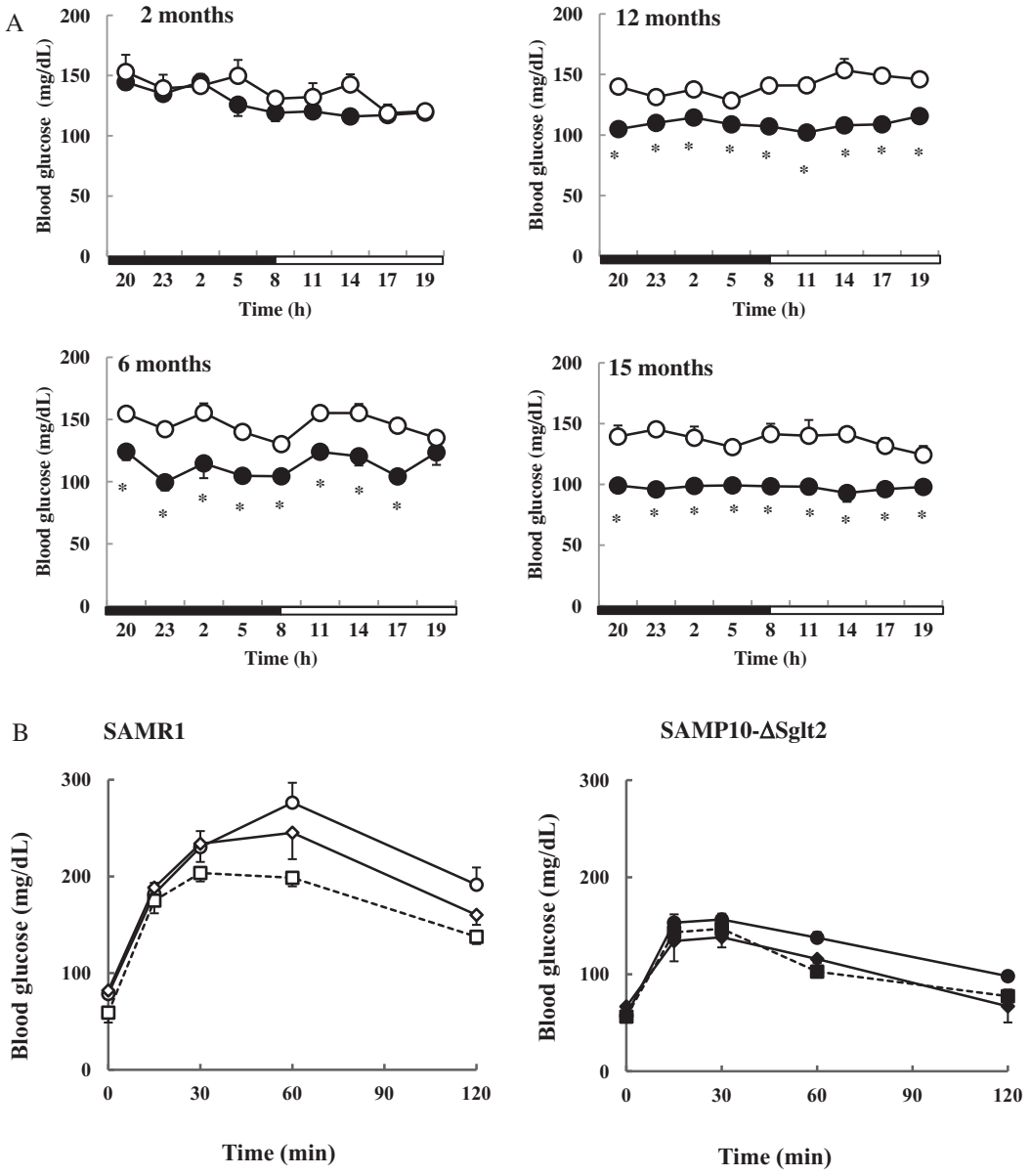

Fig. 2. Blood glucose levels of SAMP10-ΔSglt2 and SAMR1 mice. (A) Blood glucose levels were measured in 2-, 6-, 12- and 15-month-old SAMP10-ΔSglt2 (closed circle) and SAMR1 (open circle) mice allowed to feed freely. Closed and open bars in a horizontal line depict dark and light condition, respectively. Each point represents mean ± SEM (n = 3–15, $^{*}p < 0.05$). (B) Mice were fasted for 24 h then given glucose (2 g/kg weight) orally when 3 (circle), 6 (square) and 12 months (diamond) old.

GAG T-3′ [22]; SGLT1 forward 5′-CTC GTG GTG GAA CTC ATG CCT-3′, reverse 5′-CAC GTC TGG AAT GGG CTT GGT-3′; GLUT 2 forward 5′-GCC CTG ACT TCC TCT TCC AAC-3′, reverse 5′-CCT CAT TCT TTG GTG GGT GGC-3′; GLUT1 forward 5′-GCT GGG AAT CGT CGT TGG CAT-3′, reverse 5′-ACA GCT CGG CCA CAA TGA ACC-3′; β-actin forward 5′-TTG TTA CCA ACT GGG ACG ACA TGG-3′, reverse 5′-TGA TCT TGA TCT TCA TGG TGC TAG G-3′.

Genomic DNA eluted from the tail using a kit (Gentra Puregene Mouse Tail Kit, Qiagen, Tokyo, Japan) was also used for RT-PCR (sense primer, 5′-ATGGTGAGTGAGGGCTGGAAATG-3′; antisense primer, 5′-CACCTTCTCATTAACACGGGGCA-3′).

2.5. Statistical analyses

The data were expressed as the mean ± SEM. Significant differences were determined by one-way analysis of variance (ANOVA) followed by the Bonferroni test.

3. Results

3.1. Urine glucose levels and alteration in the kidney of SAMP10-ΔSglt2

In the urine of SAMP10-ΔSglt2, a remarkable amount of glucose was excreted (diagnostic tip color code: +++ (5 mg/mL) <), whereas no glucose was detected in the urine of SAMR1. Then, the total glucose excretion in urine for 24 h was measured in SAMP10-ΔSglt2 mice to which glucose was administered orally after 1 day of fasting (Fig. 1A). The total amount of urinary glucose for 24 h was almost similar among mice at 2–12 months of age. The mean concentration increased with age because urine volume was high in 2-month-old mice (2.7 ± 0.4 ml) and low in 12-month-old mice (0.6 ± 0.04 ml). In other strains of senescence-accelerated mice such as SAMP1/SkuSlc, SAMP6/TaSlc and SAMP8/TaSlc, no glucose was detected in urine. Similarly, in SAMP10/TaIdr, another

substrain of SAMP10, no glucose was detected in urine. These results indicate that glucosuria is a specific characteristic of SAMP10-ΔSglt2 mice. The kidney was innately larger in SAMP10-ΔSglt2 mice than the SAMR1 kidney (Fig. 1B). However, there was no morphological difference between both strains when 1 month old (Fig. 1C).

3.2. Blood glucose levels in SAMP10-ΔSglt2

SAMP10-ΔSglt2 mice consumed 1.24 times more food (5.91 ± 0.23 g/day) and 1.45 times more water (7.55 ± 0.39 ml/day) than SAMR1 at 6–16 months of age. The diurnal blood glucose level measured under free feeding decreased significantly in SAMP10-ΔSglt2 mice compared to SAMR1 mice at 6, 12 and 15 months of age, while the level did not differ between the two strains when they were 2 months old (Fig. 2A).

An OGTT was carried out in SAMP10-ΔSglt2 and SAMR1 mice at 3, 6 and 12 months of age. After glucose administration to SAMP10-ΔSglt2 mice fasted for 24 h, the blood glucose level increased immediately, peaked at 30 min then gradually decreased to 120 min (Fig. 2B). In SAMR1, the blood glucose level increased up to 60 min after glucose administration then decreased. The highest glucose level was about 150 mg/dL in SAMP10-ΔSglt2 mice at 30 min, and 200–280 mg/dL in SAMR1 mice at 60 min. The area under the curve (AUC) for blood glucose concentration as a function of time was significantly lower in SAMP10-ΔSglt2 (64 ± 11 mg/mL/120 min) than in SAMR1 mice (152 ± 11 mg/mL/120 min).

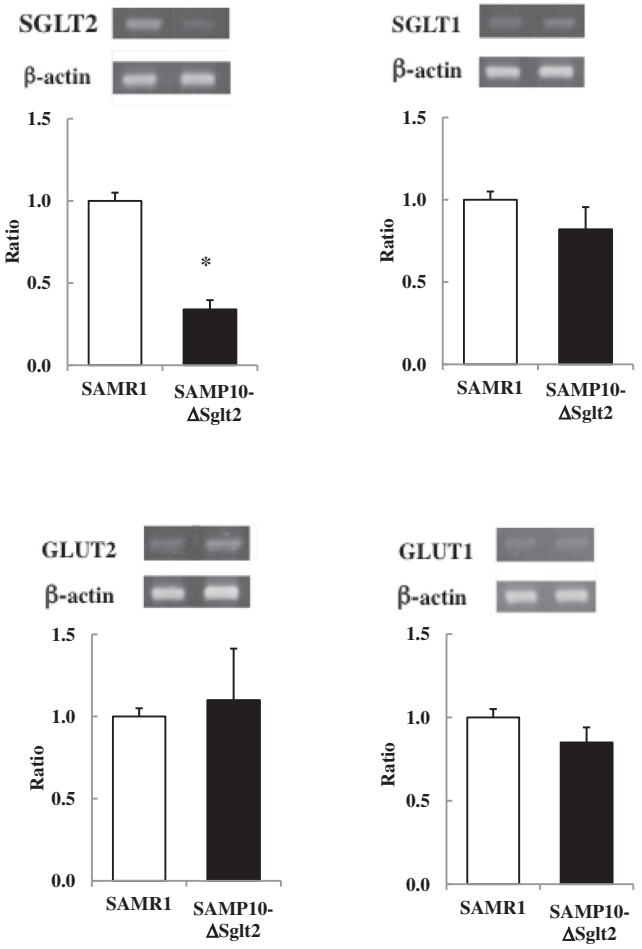

Fig. 3. Glucose transporter mRNA levels in the kidney of SAMP10-ΔSglt2 and SAMR1 mice. Representative blots of SGLT2, GLUT2, SGLT1, GLUT1 and β-actin. Relative levels of target mRNA expression were determined by normalizing individual band intensity to that of β-actin. Each column represents the mean ± SEM ($n = 3$, $^{*}p < 0.05$).

3.3. Glucose transporters in the kidney of SAMP10-ΔSglt2

In order to determine which glucose transporter is responsible for glucosuria in SAMP10-ΔSglt2 mice, we examined the expression levels of four glucose transporters in the kidney: SGLT1, SGLT2, GLUT1 and GLUT2. We identified SGLT2 as the causal factor based on significantly reduced mRNA expression in SAMP10-ΔSglt2 compared to SAMR1 mice (SAMP10-ΔSglt2, 0.34 ± 0.06; SAMR1, 1.00 ± 0.05, $n = 3$, $p < 0.001$; Fig. 3).

3.4. Identification of a single nucleotide deletion in SGLT2 in SAMP10-ΔSglt2 mice

DNA sequencing of SGLT2 in SAMP10-ΔSglt2 mice indicated a single nucleotide deletion of guanine at 1236 (Fig. 4A), which resulted in a frameshift mutation with a stop codon at 1264 with the production of a truncated protein of 421 amino acids (Fig. 4B). A deduced protein truncated from the 8th transmembrane domain is shown in Fig. 4C.

4. Discussion

A mutation in the *Slc5a2* gene encoding SGLT2 is responsible for primary renal glucosuria in humans [23]. There are two kinds of glucose transporters, GLUT and SGLT transporter families, present in the kidney. SGLTs have a role in the first step of transcellular glucose transport in the intestine and kidney. At least two sodium-coupled glucose transporters, SGLT1 and SGLT2, play an important role in the apical membrane of proximal tubular cells in the kidney [24–26]. The low-affinity/high-capacity SGLT2 mediates the bulk uptake of glucose at the early proximal tubule, and the high-affinity/low-capacity SGLT1 reduces glucose to very low concentrations in the further distal parts of the proximal tubule. After apical uptake, glucose transporters GLUT2 and GLUT1 facilitate the basolateral exit of glucose. The mutations in SGLT1 have little or no association with glucosuria [25].

In the kidney of SAMP10-ΔSglt2 mice, we found the decreased expression of SGLT2 bearing a mutation in *Slc5a2*, which may be mediated by the action of the nonsense-mediated mRNA decay pathway that eliminates mRNA transcripts containing premature stop codons. The deduced truncated form of SGLT2 in SAMP10-ΔSglt2 is speculated to be inactive. The elevation of blood glucose during OGTT was suppressed by more than an 80% reduction of the transport maximum for glucose in the kidney using a SGLT2 inhibitor [27], suggesting that glucose absorption is lowered to less than 20% in SAMP10-ΔSglt2 mice. In euglycemia, renal glucose reabsorption is mainly mediated by SGLT2 (~97%), although, under malfunction of SGLT2, the contribution of SGLT1 increases from 3% to 40–50% [28]. The defect in SGLT2 did not affect glucose homeostasis in young SAMP10-ΔSglt2 mice at 2 months of age. However, blood glucose levels significantly decreased in an age-dependent manner when mice were more than 6–15 months old. It would be interesting to study whether such compensation of SGLT1 in SAMP10-ΔSglt2 mice is compromised with aging.

Although the SGLT2 malfunction leads to a decrease in blood glucose due to renal glucose excretion, patients with primary glucosuria show a reduction in the renal tubular reabsorption of glucose with normal serum glucose levels and no impairments of tubular function [29,30]. Indeed, the discovery of SGLT2 inhibitors has offered a new therapeutic regimen for the treatment of

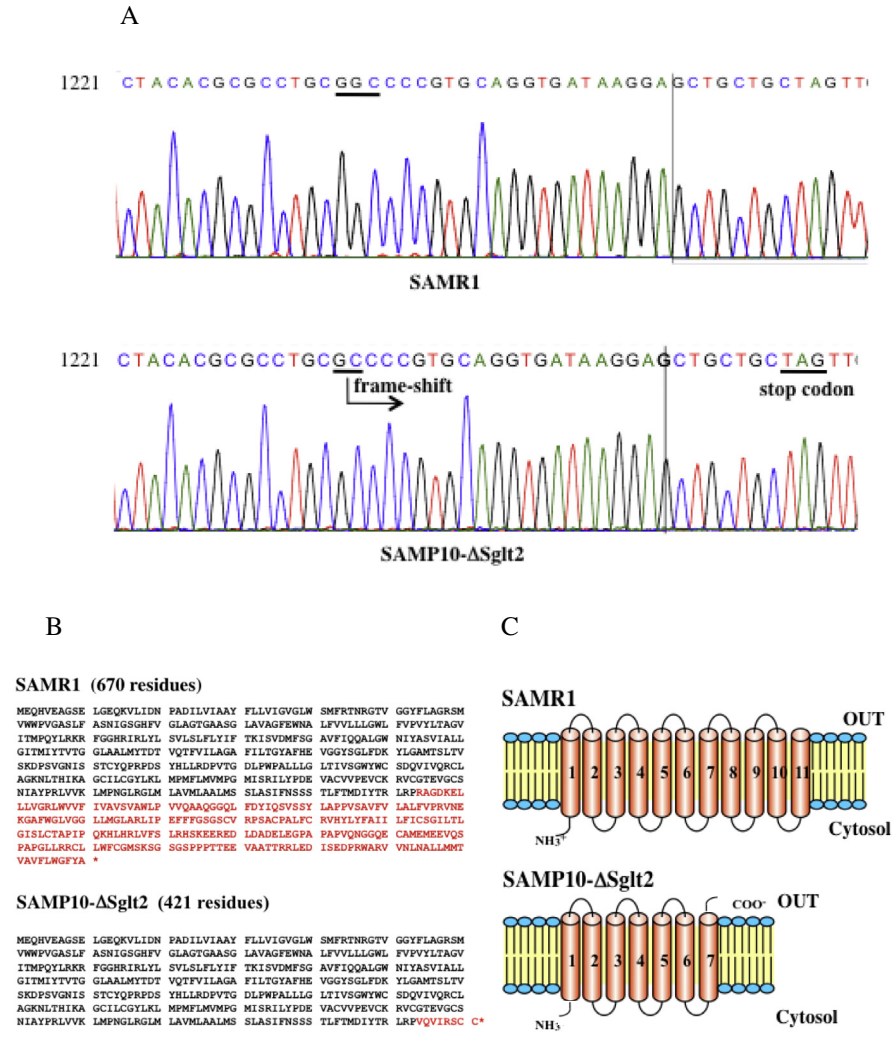

Fig. 4. Sequence of *Slc5a2* and deduced SGLT2 in SAMP10-ΔSglt2 mice. (A) DNA sequence of *Slc5a2* in SAMR1 and SAMP10-ΔSglt2 mice. (B) Amino acid sequence of SGLT2 in SAMR1 and SAMP10-ΔSglt2 mice. Asterisk depicts a stop codon. (C) Structure of SGLT2 protein in SAMR1 and a deduced model in SAMP10-ΔSglt2 mice.

patients with T2D by increasing urinary glucose excretion to remove excess glucose from the blood and help control hyperglycemia [31–34]. Insulin not only regulates blood sugar levels but also acts as a growth factor on all cells, including neurons in the central nervous system [35]. Insulin resistance is common in T2D and Alzheimer's disease (AD) [36]. Patients with T2D have a 2- to 3-fold higher risk of developing AD [37]. Cognitive deterioration is more marked in patients with AD and T2D than AD alone [38]. Furthermore, in patients with diabetes, the mean onset of dementia is 2 years earlier and survival outcomes are reported to be generally poorer [39]. These observations suggest that the treatment of T2D is critical for delaying the onset and development of AD and maintaining cognitive function. SAMP10-ΔSglt2 mice with both cognitive dysfunction and a SGLT2 mutation may serve as a unique model for studying AD and T2D.

5. Disclosures

There are no conflicts of interest to declare. All authors contributed extensively to the work presented in this paper. The conception and design of the study; K.U. Acquisition of data; H.Y., M.T., S.H., K.I., F.T., S.H.I. and M.H. Analysis and interpretation of data; K.U., M.H., K.H. and M.M. Drafting the article; K.U., M.T., A.S. and M.M.

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