

Supplemental Table 1. Primers

Gene (Species; Accession number)	Forward and Reverse Primers
Primers for mice genotyping	
Ins2 (mouse; NT_039437.7)	F: TGCTGATGCCCTGGCCTGCT
	R: TGGTCCCACATATGCACATG
Nrf2 ^{-/-} (genotyping)	Common-F: GCCTGAGAGCTGTAGGCC
	WT-R: GGAATGGAAAATAGCTCCTGCC
	Mutant-R: GACAGTATCGGCCTCAGGAA
Nrf2 ^{RPTC} Tg (genotyping)	F: GCTGGAACATTGTAGAGCTG
	R: CTGATCTCAGCTACACATTGGA
Primers for RT-qPCR	
Nrf2 (mouse/rat; NM_010902.3)	F: CGCCGCCTCACCTCTGCTGCCAGTAG
	R: AGCTCATAATCCTTCTGTCTG
Nrf2 (human; NM_006164.5)	F: ACACGGTCCACAGCTCATC
	R: TGTCATCAAATCCATGTCCTG
Sgt2 (mouse; NM_133254.4)	F: TTGGTGTGGCTTGTGGTCTAT
	R: ATGTTGCTGGCGAACAGAGA
SGLT2 (human; NM_003041.4)	F: GACACGGTACAGACCTTCGTCAT
	R: CTCCAGGTATTTGTGGAAGAGA
Agt (mouse/rat; NM_031144.3)	F: CCACGCTCTCTGGATTTATC
	R: ACAGACACCGAGATGCTGTT
TGF-β1 (mouse; NM_011577)	F: CCAAATAAGGCTCGCCAGTC
	R: GGCAGTCTCCCGAATGTC
Fn1 (mouse; NM_001276413.1)	F: TAGCAGGCTACCGACTGACCG
	R: CACCCAGCTTGAAGCCAATCC
Cat (mouse; NM_009804.2)	F: CGACCAGATGAAGCAGTGGA
	R: CCACTCTCTCAGGAATCCGC
Nox4 (mouse; NM_015760.4)	F: TGGCCAACGAAGGGGTTAAA
	R: GATGAGGCTGCAGTTGAGGT
β-actin (human/mouse/rat; NM_031144.3)	F: ACGATTTCCCTCTCAGCTT
	R: TACAATGAGCTGCGTGTGGC

Supplemental Table 1. Primers (continued)

Gene (Species; Accession number)	Forward and Reverse Primers
Primers for Sglt2 promoter site-directed mutation	
del hSGLT2 (-1316)-ARE	F: ACTGTA CTCCAGCTTTGGAAGAC CTGTCTCAAAC R: GTTTTGAGACAGGGTCTTCAAAGCTGGAGTACAGT
del mSglt2 (-1527)-ARE	F: AGGTTCTCAGGCATTTTGGGATGGGTCCCATTTC R: GAAATGGGACCCATCCCAAATGCCTGAGAACCT
Primers for truncated Sglt2 promoters	
mSglt2 (-1952)-F	GGACATCACATGGTACCAAAC
mSglt2 (-1248)-F	AAATTGGTACCGATGCAGGTTCTATACAGGAG
mSglt2 (-235)-F	AAATTGGTACCGCTTGAACACTGGGTATAG
mSglt2 (-684)-(xhoI)-R	TTTCTCGAGCACCAACTGTGCCTCTATT
hSGLT2 (-1285)-F	GAAACACATGCTTTGTTGG
hSGLT2 (-194)-F	TAAGGCCAGGAAAGAGTGC
hSGLT2 (-1986)-(XhoI)-F	ttaaCTCGAGGTCTGTAAACACACAGTGC
hSGLT2 (+17)-(BglII)-R	aattAGATCTCATTCTCCCAGGATCTGC
Primers for EMSA	
hSGLT2 promoter	
BIO-GS-hSGLT2 (-1316)	F: AGCTTTGGTGACACAGCAAGACCCTGT R: ACAGGGTCTTGCTGTGTACCAAAGCT
hSGLT2 (-1316) WT	F: AGCTTTGGTGACACAGCAAGACCCTGT R: ACAGGGTCTTGCTGTGTACCAAAGCT
hSGLT2 (-1316) MUT1	F: AGCTTTGGaatCACAGCAAGACCCTGT R: ACAGGGTCTTGCTGTGATTCAAAGCT
hSGLT2 (-1316) MUT2	F: AGCTTTGGaatCACaAaAAGACCCTGT R: ACAGGGTCTTTTTGTGATTCAAAGCT
hSGLT2 (-1316) MUT3	F: AGCTTTGGaataaaaaaAAGACCCTGT R: ACAGGGTCTTTTTTTATTCAAAGCT
mSglt2 promoter	
BIO-GS-mSglt2 (-1527)	F: GACCCATCCCTGACACTGCTAAAATGCCTGA R: TCAGGCATTTTAGCAGTGTGAGGGATGGGTC
mSglt2 (-1527) WT	F: GACCCATCCCTGACACTGCTAAAATGCCTGA R: TCAGGCATTTTAGCAGTGTGAGGGATGGGTC
mSglt2 (-1527) MUT1	F: GACCCATCCCaataaaaaTAAAATGCCTGA R: TCAGGCATTTTAtttttattGGGATGGGTC
mSglt2 (-1527) MUT2	F: GACCCATCCCaatCACTaaTAAAATGCCTGA R: TCAGGCATTTTAttAGTattGGGATGGGTC
mSglt2 (-1527) MUT3	F: GACCCATCCCaatCACTGCTAAAATGCCTGA R: TCAGGCATTTTAGCAGTattGGGATGGGTC
Primers for ChIP assay	
ChIP-SGLT2 (177)	F: CCAGCTATTTGGGAAGCTGA
ChIP-SGLT2 (400)	R: TGTGCAACGACTTTCCTGAG

Supplemental Table 2. Antibodies for Western Blotting

Antibody (Host)	WB/IHC (Dilution)	Suppliers
Nrf2 (mouse monoclonal, ab89443)	WB(1:2000)	Abcam
Nrf2 (rabbit polyclonal, ab31163)	IHC (1:400)	Abcam
Nrf2 (rabbit monoclonal, ab62352)	Chip grade (1)	Abcam
NQO-1 (mouse monoclonal, ab28947)	IHC (1:400)	Abcam
Keap 1 (rabbit polyclonal, ab66620)	IHC (1:400)	Abcam
Sgt2 (D-6, mouse monoclonal, sc-393350)	WB (1:2000)	Santa Cruz Biotechnology
Sgt2 (rabbit polyclonal, ab85626)	IF (1:400)	Abcam
Agt (rabbit polyclonal ²)	WB (1:2000); IHC (1:200)	Generated in our lab
TGF- β 1 (rabbit polyclonal, sc-146)	IHC (1:200)	Santa Cruz Biotechnology
Histone H3 (rabbit monoclonal, CST4620s)	Chip grade	Cell signaling
IgG (rabbit polyclonal, CST2729P)	Chip grade	Cell signaling
Myc-Tag (mouse monoclonal, 9B11)	Chip grade	Cell signaling
β -actin (mouse monoclonal, a5441)	WB (1:10000)	Sigma

(1) Use of this antibody is as described in the supplemental methods.

(2) Wang L, Lei C, Zhang et al. Synergistic effect of dexamethasone and isoproterenol on the expression of angiotensinogen in immortalized rat proximal tubular cells. *Kidney International* 53:287-295, 1998.

Supplemental Table 3. Patient Characteristics

Patient ID	a	b	c	d	e	f	g	h
Diabetes (Non/Yes)	Non	None	None	None	Yes (Type 2)	Yes (Type 2)	Yes (Type 2)	Yes (Type 2)
Age (y)	38	50	63	64	67	53	80	65
Sex (M or F)	F	F	F	M	M	M	M	M
Serum creatinine (mg/dL)	0,54	0,76	0,74	0,80	1,71	1,02	1,73	1,74
Serum glucose (mg/dL)	97,3	100,9	102,7	97,0	232,4	195,6	228,8	200,0
Urine glucose	0	0	0	0	6 mmol/L	3 mmol/L	17 mmol/L	56 mmol/L
Urine protein*	0	0	0	0	2,65 g/L (2)	0	1,5 g/L	0,73 g/L
GFR (mL/min)**	140	86	85	92	40	81	38	73
Known drugs used	ARB	None	None	ARB/HCT2	***	****	*****	*****
Hypertension (Yes or No)	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Diagnosis	Papillary variant carcinoma	Clear cell carcinoma	Renal carcinoma (1)	Clear cell carcinoma	Papillary variant carcinoma	Clear cell carcinoma	Clear cell carcinoma	Clear cell carcinoma

*Urine protein is determined on dipstick.

**GFR is calculated with MDRD equation.

(1) with changes suggestive of renal carcinoma, thyroid-like

(2) obtained with urinary collect

***Diuretic, ARB, insulin, Beta-blocker, Calcium Channel Blocker

****Diuretic, Angiotensin Receptor Blocker, antineoplastic agent, oral hypoglycemic agent, Beta-blockers, Calcium Channel Blockers

***** ACEI, Oral hypoglycemic agent, Beta-blocker

Supplemental Figure 1

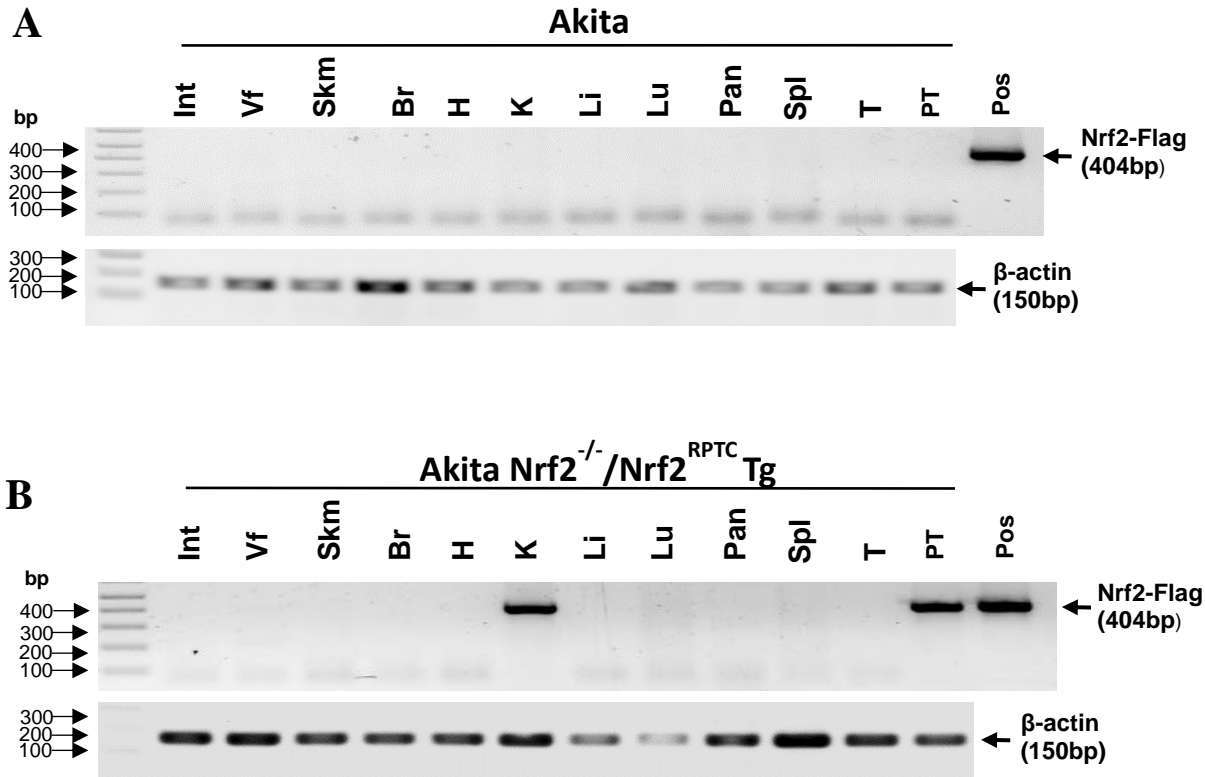


Figure 1. PCR product showing tissue expression of *rNrf2-Flag* mRNA in male Akita (A) and Akita *Nrf2^{-/-}/Nrf2^{RPTC}* Tg mice (B). *rNrf2-Flag* (404 bp) and *β-actin* (150 bp) fragments are indicated. Int: intestine; Vf: Visceral fat; Skm: Skeletal muscle; Br, brain; H, heart; Ki, kidney; Li, liver; Lu, lung; Pan, pancreas; Spl, spleen; T, testis; PT, isolated proximal tubule; Pos, positive Nrf2 plasmid control.

Supplemental Figure 2

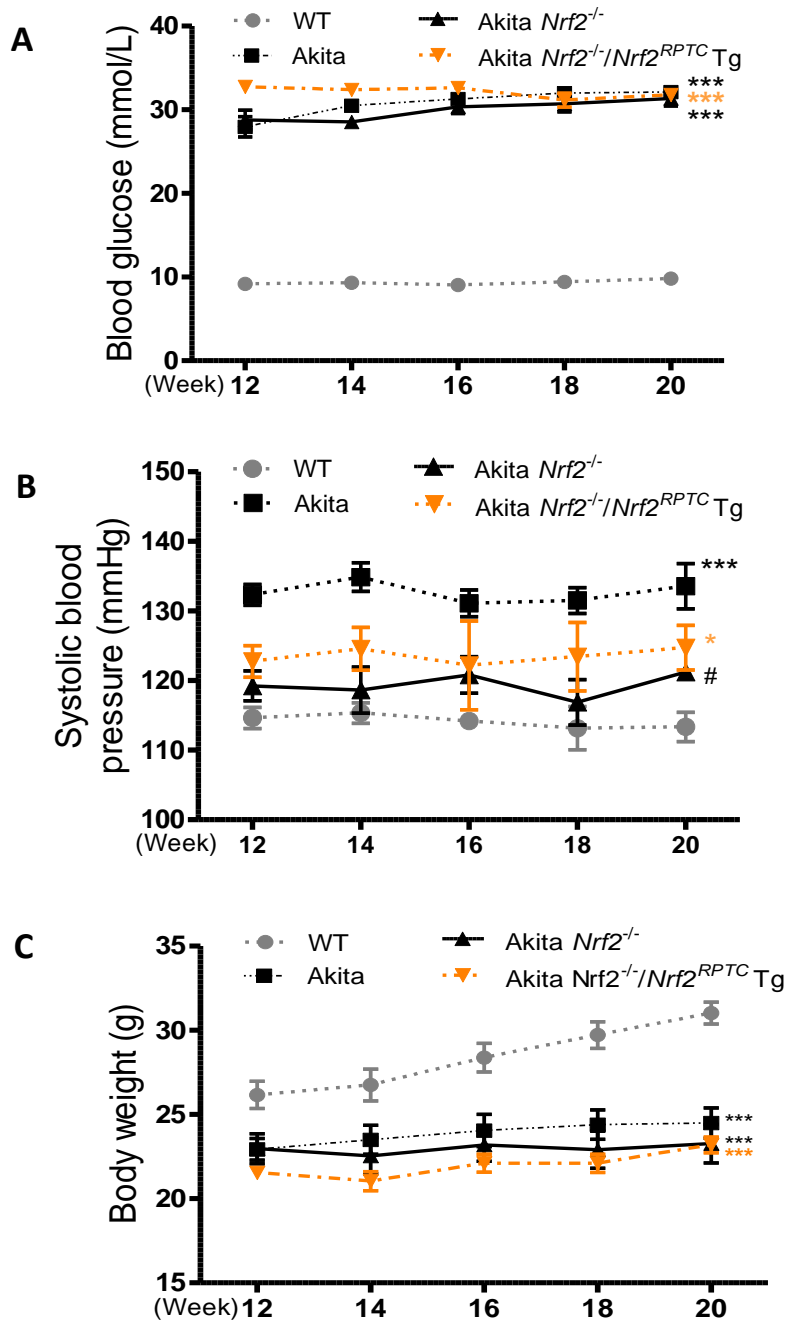


Figure 2. Longitudinal blood glucose (BG, A), systolic blood pressure (SBP, B) and body weight (BW, C) of WT, Akita, Akita *Nrf2*^{-/-} and Akita *Nrf2*^{-/-}/*Nrf2*^{RPTC} Tg mice. BG level, SBP and BW were recorded every two weeks starting week 12 to week 20. BG and SBP were measured by glucometer (Accu-Chek Performa System) and BP-2000 Tail-cuff Pressure Monitor, respectively. All data are expressed as means ± SEM. n=9 mice per group; Statistics were done at 20 weeks by one-way ANOVA, followed by Bonferroni *post-hoc* test. *p<0.05; ***p<0.005 vs. WT; #P < 0.05 vs. Akita.

Supplemental Figure 3

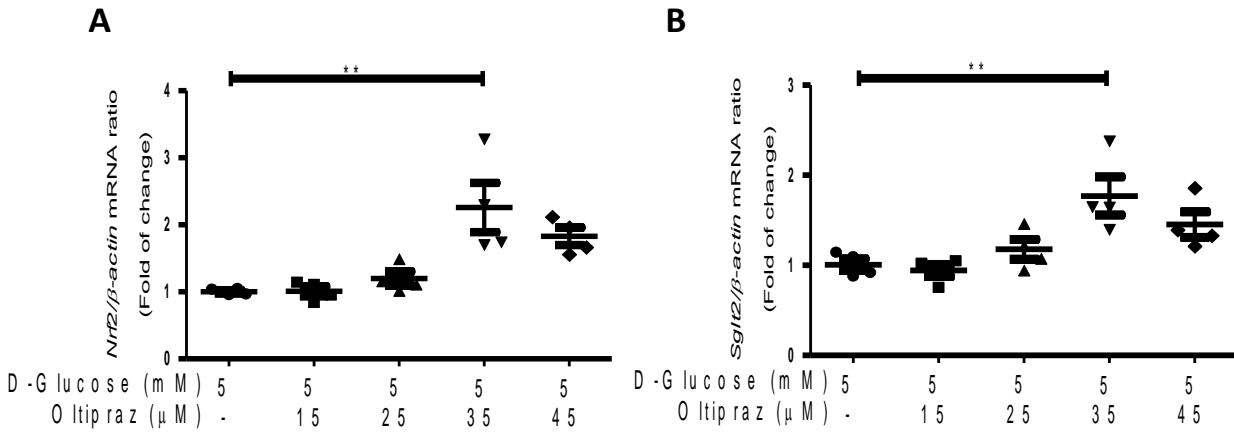


Figure 3. Oltipraz stimulates expression of *Nrf2* mRNA and *Sgl2* mRNA in a dose-dependent manner in HK2 cells. Cells were incubated with oltipraz at different dose for 24 hours in normal glucose (5 mM). All data are expressed as means \pm SEM. n=4 per group. Statistics were done by one-way ANOVA, followed by Bonferroni *post-hoc* test. **P < 0.01 vs 5mM D-Glucose.

Supplemental Figure 4

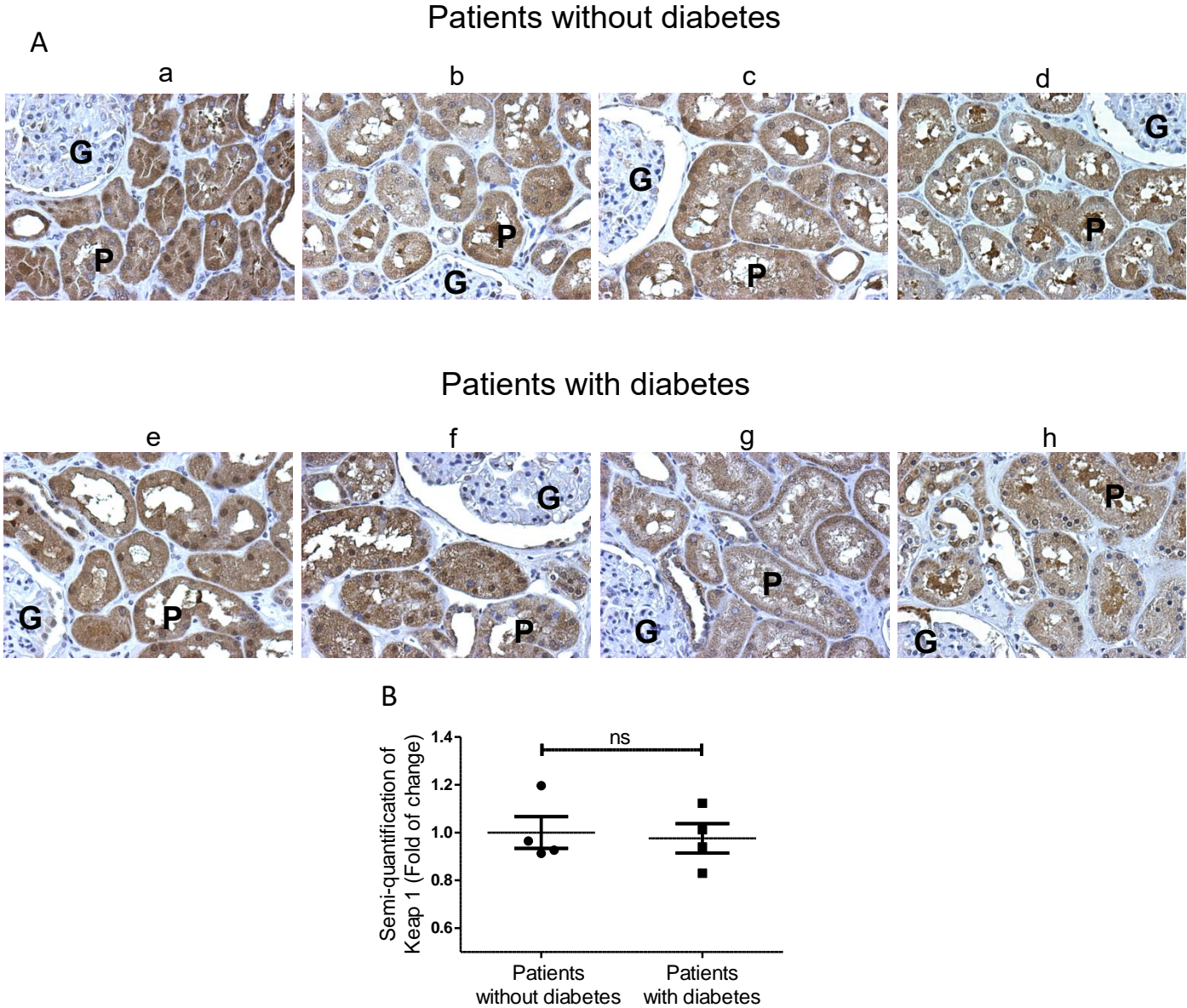


Figure 4. IHC staining of KEAP 1 (A) and semi-quantification (B) in patients without and with diabetes (G, glomerulus; and P, proximal tubule; X200). Statistic was done by *unpaired t-test* for figure B. ns, not significant.