

Table S1. The primer sequences for genotyping of rs13306393

Genotyping primers	5'-3'
Forward Primer	GCCCAGACAGCCTTGACTCT
Reverse Primer	GCTGCTCTCCCAGTGCAAAG
Probe Reporter 1	TAAGGGTCACACAAA
Probe Reporter 2	TAAGGGTCACTCAAAG

Table S2. The characteristics of subjects with or without rs13306393A in the association analysis with rs780094

	Subjects with rs13306393A (n = 81)	Subjects without rs13306393A (n = 162)
Age, years	49.7 ± 12.0	49.7 ± 11.8
Gender, male/female	36/45	71/91
Diabetes, n (%)	28 (34.6)	56 (34.6)
Prediabetes, n (%)	37 (45.7)	74 (45.7)
Controls, n (%)	16 (19.8)	32 (19.8)
rs780094 A/A, n (%)	21 (25.9)	36 (22.2)
rs780094 A/G, n (%)	42 (51.9)	97 (59.9)
rs780094 G/G, n (%)	18 (22.2)	29 (17.9)
MAF of rs780094	0.481	0.478

In our study, we found subjects who carried the A allele of rs13306393 of GCK have very similar phenotypes to subjects who carried variants of glucokinase regulatory protein (GCKR) (rs780094). In order to investigate whether subjects who carried the A allele of rs13306393 also carried this GCKR variant and the association between them, all 81 samples with the A allele of rs13306393 and 162 samples without A allele in Samples 1 were selected. These two groups were exactly matched by sex, age, and glucose tolerance condition.

In the group with A allele of rs13306393, there are 21 samples with the A/A for rs780094, 42 samples with A/G for rs780094, and 18 samples with G/G for rs780094 (MAF = 0.481). And in the matched group without A allele of rs13306393, there are 36 samples with A/A for rs780094, 97 samples with A/G for rs780094, 29 samples with G/G for rs780094 (MAF = 0.478). The distribution was nearly the same in the two groups ($p = 0.923$). So, the effect of rs13306393 is independent of rs780094 although the phenotypes were like the rs780094.

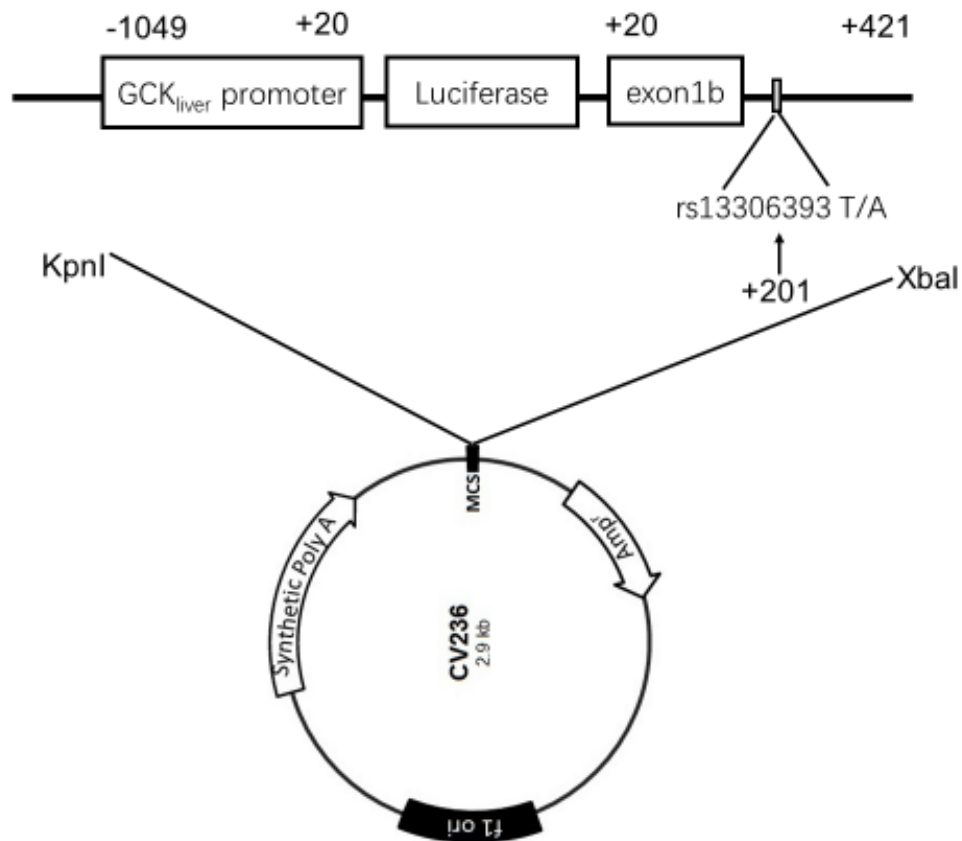


Figure S1. The diagram of the GCK_{Liver}-promoter-Luc-rs13306393 T/A reporter.

Human GCK liver-specific 5'-flanking sequence spanning bases -1049 to +20 relative to the liver-specific mRNA start site (NM_033507), reported as hepatic GCK promoter, the luciferase reporter gene, and the sequence spanning bases +21 to +421 including exon 1b and the exon-intron boundaries with the GCK-rs13306393 T or GCK-rs13306393 A were synthesized in the order (GCK_{Liver} promoter-luciferase-exon1b-intron1). Then the sequence was construct to the CV236 luciferase reporter plasmid (purchased from Shanghai Genechem Co, Ltd.) to get two reporters (GCK_{Liver}-promoter-Luc-rs13306393 T and GCK_{Liver}-promoter-Luc-rs13306393 A).

The sequence of GCK_{Liver}-promoter-Luc-rs13306393 T/A

Annotation: Human GCK liver-specific 5'-flanking sequence spanning bases -1049 to +20 relative to the liver-specific mRNA start site (NM_033507) was shown in green font. The sequence of luciferase was shown in black font. The sequence spanning bases +21 to +421 including exon 1b and the exon-intron boundaries with the GCK-rs13306393 T or GCK-rs13306393 was shown in blue font.

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CCACTTGCCTCAGCTTCAGGCTTTGTACACATCCTCAGCCTTTCTTGAGAACTGAATTTAGATTC
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GACGGAAAAAGAGATCGTGGATTACGTCGCCAGTCAAGTAACAACCGCGAAAAAGTTGCGCG
GAGGAGTTGTGTTTGTGGACGAAGTACCGAAAGGTCTTACCGGAAAACTCGACGCAAGAAAA
ATCAGAGAGATCCTCATAAAGGCCAAGAAGGGCGGAAAGATCGCCGTGTAATTCTAGTCAGC
CTCAGGCAGCTCTCCATCCAAGCAGCCGTTGCTGCCACAGGCGGGCCTTACGCTCCAAGGCTA
CAGCATGTGCTAGGCCTCAGCAGGCAGGAGCATCTCTGCCTCCCAAAGCATCTACCTCTTAGC
CCCTCGGAGAGATGGCGATGGATGTACAAGGAGCCAGGCCAGACAGCCTTGACTCTGGTAA
GGGTAC(A/T)CCAAAGTTAGGGACTTTGCACTGGGAGAGCAGCACCCAGGGCAGGGCCCTTG
GTTTTGCAGATTACCAAACTAAGGCTGGGGGCAGGGAAGGCGAGCAGGCTTGGGGCACCTT
GGAAGGAGGCACATGGGCCTTGGGGGTCTGGCTAGGGCAGCTGTGCCTGCCACTGGCCCTCT
GCCACCACCCTCCTCACTGTG



Figure S2. LD plot between rs13306393 and the SNPs which were reported associated with diabetes or diabetes-related traits in Chinese.

The genotype data across the GCK gene (GRCh37: 1000G_chr7_44183870-44229022) for Han Chinese were extracted from the 1000Genomes database

(<https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/>) and explored the LD using HaploView software (version 4.2).

The color of block was displayed as standard (D'/LOD). If the value of D'/LOD is larger, the color of block is darker. The number in the block was the value of D' .

Table S3. LOD between rs13306393 and the SNPs which were reported associated with diabetes or diabetes-related traits in Chinese

L1	L2	D'	LOD	r ²	CI _{low}	CI _{hi}	Dist	T-int
rs2268576(1)	rs13306393	1	0.48	0.028	0.08	0.98	9637	-
rs2971677(2)	rs13306393	0.999	0.07	0.005	0.04	0.97	6400	47.49
rs13306393	rs12673242(1)	1	0.12	0.006	0.04	0.97	8834	49.33
rs13306393	rs2908290(3)	1	0.25	0.013	0.05	0.97	17477	-
rs13306393	rs2300587(3)	0.902	0.06	0.004	0.04	0.97	20134	-
rs13306393	rs730497(4)	0.452	0.2	0.012	0.04	0.86	25061	-
rs13306393	rs2908289(5)	0.452	0.2	0.012	0.04	0.86	25282	-
rs13306393	rs2268569(3)	0.019	0	0	0.01	0.7	28360	-
rs13306393	rs1799884(3; 6-10)	0.443	0.18	0.011	0.04	0.86	30408	-
rs13306393	rs193226243(6)	1	0.01	0	0.04	0.96	31254	-
rs13306393	rs1476891(6)	1	0.13	0.006	0.05	0.97	31308	-
rs13306393	rs3757840(11)	1	0.09	0.017	0.04	0.97	32556	-
rs13306393	rs6975024(12)	0.443	0.18	0.011	0.04	0.86	33226	-
rs13306393	rs741036(3)	0.144	0.04	0.002	0.02	0.71	36053	-
rs13306393	rs2908286(2)	0.443	0.18	0.011	0.04	0.86	36077	-
rs13306393	rs4607517(6; 13; 14)	0.443	0.18	0.011	0.04	0.86	37008	-

The genotype data across the GCK gene for Han Chinese we extracted from the 1000Genomes database (<https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/>) and explored the LD using HaploView software (version 4.2).

Reference

1. Hernandez-Escalante VM, Nava-Gonzalez EJ, Voruganti VS, Kent JW, Haack K, Laviada-Molina HA, Molina-Segui F, Gallegos-Cabriaes EC, Lopez-Alvarenga JC, Cole SA, Mezzles MJ, Comuzzie AG, Bastarrachea RA: Replication of obesity and diabetes-related SNP associations in individuals from Yucatan, Mexico. *Frontiers in genetics* 2014;5:380
2. Bien SA, Pankow JS, Haessler J, Lu Y, Pankratz N, Rohde RR, Tamuno A, Carlson CS, Schumacher FR, Buzkova P, Daviglus ML, Lim U, Fornage M, Fernandez-Rhodes L, Aviles-Santa L, Buyske S, Gross MD, Graff M, Isasi CR, Kuller LH, Manson JE, Matisse TC, Prentice RL, Wilkens LR, Yoneyama S, Loos RJF, Hindorff LA, Le Marchand L, North KE, Haiman CA, Peters U, Kooperberg C: Transethnic insight into the genetics of glycaemic traits: fine-mapping results from the Population Architecture using Genomics and Epidemiology (PAGE) consortium. *Diabetologia* 2017;60:2384-2398
3. Rasmussen-Torvik LJ, Guo X, Bowden DW, Bertoni AG, Sale MM, Yao J, Bluemke DA, Goodarzi MO, Chen YI, Vaidya D, Raffel LJ, Papanicolaou GJ, Meigs JB, Pankow JS: Fasting glucose GWAS candidate region analysis across ethnic groups in the Multiethnic Study of Atherosclerosis

(MESA). *Genet Epidemiol* 2012;36:384-391

4. Ohshige T, Iwata M, Omori S, Tanaka Y, Hirose H, Kaku K, Maegawa H, Watada H, Kashiwagi A, Kawamori R, Tobe K, Kadowaki T, Nakamura Y, Maeda S: Association of new loci identified in European genome-wide association studies with susceptibility to type 2 diabetes in the Japanese. *PLoS one* 2011;6:e26911

5. Choi JW, Moon S, Jang EJ, Lee CH, Park JS: Association of prediabetes-associated single nucleotide polymorphisms with microalbuminuria. *PLoS one* 2017;12:e0171367

6. Muller YL, Piaggi P, Hoffman D, Huang K, Gene B, Kobes S, Thearle MS, Knowler WC, Hanson RL, Baier LJ, Bogardus C: Common genetic variation in the glucokinase gene (GCK) is associated with type 2 diabetes and rates of carbohydrate oxidation and energy expenditure. *Diabetologia* 2014;57:1382-1390

7. Liu CT, Ng MC, Rybin D, Adeyemo A, Bielinski SJ, Boerwinkle E, Borecki I, Cade B, Chen YD, Djousse L, Fornage M, Goodarzi MO, Grant SF, Guo X, Harris T, Kabagambe E, Kizer JR, Liu Y, Lunetta KL, Mukamal K, Nettleton JA, Pankow JS, Patel SR, Ramos E, Rasmussen-Torvik L, Rich SS, Rotimi CN, Sarpong D, Shriner D, Sims M, Zmuda JM, Redline S, Kao WH, Siscovick D, Florez JC, Rotter JJ, Dupuis J, Wilson JG, Bowden DW, Meigs JB: Transferability and fine-mapping of glucose and insulin quantitative trait loci across populations: CARE, the Candidate Gene Association Resource. *Diabetologia* 2012;55:2970-2984

8. Grimsby JL, Porneala BC, Vassy JL, Yang Q, Florez JC, Dupuis J, Liu T, Yesupriya A, Chang MH, Ned RM, Dowling NF, Khoury MJ, Meigs JB, Investigators M: Race-ethnic differences in the association of genetic loci with HbA1c levels and mortality in U.S. adults: the third National Health and Nutrition Examination Survey (NHANES III). *BMC medical genetics* 2012;13:30

9. Tarnowski M, Malinowski D, Pawlak K, Dziedziejko V, Safranow K, Pawlik A: GCK, GCKR, FADS1, DGKB/TMEM195 and CDKAL1 Gene Polymorphisms in Women with Gestational Diabetes. *Canadian journal of diabetes* 2017;41:372-379

10. Tam CH, Ho JS, Wang Y, Lee HM, Lam VK, Germer S, Martin M, So WY, Ma RC, Chan JC, Ng MC: Common polymorphisms in MTNR1B, G6PC2 and GCK are associated with increased fasting plasma glucose and impaired beta-cell function in Chinese subjects. *PLoS one* 2010;5:e11428

11. Weedon MN, Clark VJ, Qian Y, Ben-Shlomo Y, Timpson N, Ebrahim S, Lawlor DA, Pembrey ME, Ring S, Wilkin TJ, Voss LD, Jeffery AN, Metcalf B, Ferrucci L, Corsi AM, Murray A, Melzer D, Knight B, Shields B, Smith GD, Hattersley AT, Di Rienzo A, Frayling TM: A Common Haplotype of the Glucokinase Gene Alters Fasting Glucose and Birth Weight: Association in Six Studies and Population-Genetics Analyses. *The American Journal of Human Genetics* 2006;79:991-1001

12. Stancakova A, Laakso M: Genetics of Type 2 Diabetes. *Endocr Dev* 2016;31:203-220

13. Jung SY, Sobel EM, Papp JC, Crandall CJ, Fu AN, Zhang ZF: Obesity and associated lifestyles modify the effect of glucose metabolism-related genetic variants on impaired glucose homeostasis among postmenopausal women. *Genet Epidemiol* 2016;40:520-530

14. Balakrishnan P, Navas-Acien A, Haack K, Vaidya D, Umans JG, Best LG, Goessler W, Francesconi KA, Franceschini N, North KE, Cole SA, Voruganti VS, Gribble MO: Arsenic-gene interactions and beta-cell function in the Strong Heart Family Study. *Toxicol Appl Pharmacol* 2018;348:123-129