PNAS LETTER

The human glucose and lipid homeostasis–associated genetic polymorphisms do not regulate *SLC25A47* gene expression in the liver

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Transporters of the mitochondrial carrier superfamily (SLC25), with 53 members, play a crucial role in maintaining metabolic homeostasis (1). Expression of the SLC25 family varies greatly among tissues, and SLC25A47 is a liver-specific mitochondrial carrier (1–3). Recently, Yook et al. identify that 9 single-nucleotide polymorphisms (SNPs) in *SLC25A47* are significantly associated with glucose and lipid homeostasis, such as fasting glucose, random glucose, HbA1c, and high-density lipoprotein cholesterol levels in humans (1). However, whether and how these SNPs affect *SLC25A47* gene expression remains unknown, which has prompted us to explore the findings further.

First, linkage disequilibrium (LD) among these 9 SNPs is calculated on the basis of the 1000 Genomes European panel (4–7). Interestingly, similar to our previous study (8), the LD analysis indicates that rs1535464, rs35097172, rs1951519, rs3736952, and rs8015259 are in high LD with each other (r^2 range = 0.64 to 0.96), while rs34184867, rs35007880, rs3736951, and rs7147511 are in strong LD with each other (r^2 range = 0.91 to 0.99) (Fig. 1). In addition, we compare allele frequencies of the 9 SNPs in Africans (AFR), Americans (AMR), East Asians (EAS), Europeans (EUR), and South Asians (SAS) descent from the 1000 genomes project. The results show that frequencies of rs1535464, rs35097172, rs1951519, rs3736952, and rs8015259 are identical or nearly identical in the same ethnicity, and frequencies of rs34184867, rs35007880, rs3736951, and rs7147511 are identical or nearly identical in the same ethnicity (Table 1). These results indicate that the 9 SNPs are not independent of each other.

Because SLC25A47 is selectively expressed in the liver of humans, then we evaluate the association of these 9 SNPs with *SLC25A47* expression using expression quantitative trait loci (eQTL) datasets from the Genotype-Tissue Expression (GTEx) project in the liver (9, 10). The eQTL analysis is performed by applying the linear regression based on an additive model. The results show that all effect alleles of the 9 SNPs could regulate a reduced *SLC25A47* expression in the liver ($\beta < 0$), except for rs1951519 ($\beta = 0.004$). However, the association between the 9 SNPs and *SLC25A47* expression does not pass the significance level of 0.05. More detailed results are presented in Table 1.

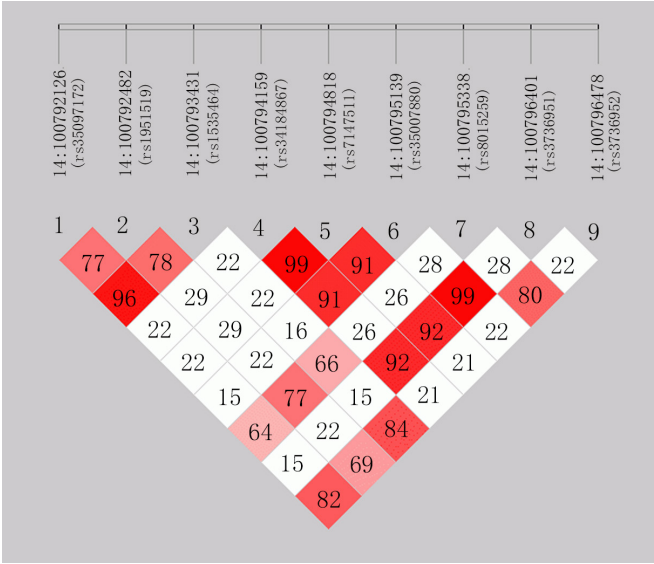

Fig. 1. The LD analysis for the nine *SLC25A47* SNPs r^2-value (×100).

In summary, Yook et al. independently found that SLC25A47 is selectively expressed in the liver of humans and significant associations of *SLC25A47* genetic variants with glycemic and lipid homeostasis. Here, we show that all the associated SNPs

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Table 1. The metabolic phenotypes-associated SNPs and SLC25A47 gene expression in the liver of human

			1000G Allele Frequencies					GTEx Association		
SNPs	EA	NEA	AFR (%)	AMR (%)	EAS (%)	EUR (%)	SAS (%)	β*	SE	*P*-Value†
rs1535464	A	G	7	12	12	21	16	−0.013	0.057	0.82
rs35097172	T	C	7	12	12	21	16	−0.012	0.060	0.84
rs1951519	A	C	48	16	24	25	19	0.004	0.054	0.95
rs3736952	T	C	7	12	13	19	17	−0.012	0.057	0.83
rs8015259	C	G	50	16	25	23	20	−0.038	0.055	0.49
rs34184867	G	C	6	31	23	47	66	−0.025	0.048	0.60
rs35007880	T	G	4	31	23	49	66	−0.030	0.048	0.53
rs3736951	T	C	4	31	23	49	66	−0.030	0.048	0.53
rs7147511	T	C	4	31	23	47	66	−0.032	0.048	0.51

EA, effect allele; NEA, nonEA. AFR, AMR, EAS, EUR, and SAS. SE standard error.
*β is the regression coefficient based on the EA. $\beta > 0$ and $\beta < 0$ indicate that the effect/mutant allele regulates increased and reduced gene expression, respectively.
†The threshold of statistical significance for eQTLs analysis was $P < 0.05$.

could not significantly regulate reduced *SLC25A47* gene expression in the liver. We believe that our findings provide important supplementary information about the role of *SLC25A47* genetic variants in gluconeogenesis and energy expenditure.

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