Genetic variant rs17185536 regulates *SIM1* gene expression in human brain hypothalamus

Guiyou Liu[a,b,c], Yang Hu[c], Zhifa Han[c], Shuilin Jin[d,1], and Qinghua Jiang[c,1]

Recently in PNAS, Jorgenson et al. (1) conducted a large-scale genome-wide association study (GWAS) to identify genetic variants associated with erectile dysfunction. In the discovery stage, Jorgenson et al. (1) analyze the erectile dysfunction GWAS dataset in 36,649 men in the multiethnic Kaiser Permanente Northern California Genetic Epidemiology Research in Adult Health and Aging cohort. They identify the genetic variant rs17185536 on chromosome 6 near the single-minded family basic helix-loop-helix transcription factor 1 (*SIM1*) gene to be significantly associated with the risk of erectile dysfunction (odds ratio for T allele = 1.26, $P = 3.40E-25$) (1). In the replication stage, Jorgenson et al. (1) analyze the erectile dysfunction GWAS dataset in 222,358 men from the UK Biobank, and replicated this association (odds ratio for T allele = 1.25, $P = 6.80E-14$).

It has been reported that mouse *Sim1* is expressed in the developing kidney and central nervous system (2–4). Jorgenson et al. (1) further test the enhancer activity of rs17185536 risk and reference alleles in human embryonic kidney 293T cells (1). They find that compared with empty vector, the rs17185536-T (risk) allele has significant enhancer activity and the rs17185536-C (reference) allele does not (1). Jorgenson et al. (1) conclude that the rs17185536-T allele or other erectile dysfunction-associated alleles in this region may regulate the expression of *SIM1*. However, Jorgenson et al. (1) do not directly evaluate the association of rs17185536 with the expression of *SIM1*. Until now, it remains unclear about the association of rs17185536 variant with the expression of *SIM1*.

Here, we evaluated the association between rs17185536 and *SIM1* expression using two expression quantitative trait loci (eQTLs) datasets. The first eQTLs dataset is from the NephQTL database, including the human kidney tissues glomerulus ($n = 136$) and tubulointerstitium ($n = 166$) in the Nephrotic Syndrome Study Network cohort (5). MatrixEQTL was used to perform the eQTLs analysis in glomerulus and tubulointerstitium (5). The second eQTLs dataset is from the Genotype-Tissue Expression (GTEx) Project (version 7), which included 11,688 samples, 53 tissues, and 714 donors (6). In GTEx, a linear regression analysis was applied to perform the eQTLs analysis using FastQTL, assuming an additive model and adjusting for several critical covariates, including top 3 genotyping principal components; genotyping platform; 15, 30, 45, and 60 probabilistic estimation of expression residuals factors; and male sex (6–9). The significance level was defined as $P < 0.05$.

In the NephQTL database, the results showed no significant association between rs17185536 and *SIM1* expression in the human kidney tissues glomerulus and tubulointerstitium (Table 1). In GTEx (version 7), rs17185536 is available in only 10 of 53 tissues. The results showed that the rs17185536-T allele could significantly regulate increased expression of *SIM1* in transformed fibroblast cells ($P = 1.61E-02$) and human brain hypothalamus ($P = 6.69E-04$) (Table 1). Importantly, the association between rs17185536 and *SIM1* expression passed the multiple testing correction threshold of $0.05/12 = 4.17E-03$.

In summary, our findings highlight the association between rs17185536 and *SIM1* expression in human brain hypothalamus and may provide important information about the role of rs17185536 in erectile dysfunction.

[a]Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing 100053, China; [b]Beijing Institute for Brain Disorders, Capital Medical University, Beijing 100054, China; [c]School of Life Science and Technology, Harbin Institute of Technology, Harbin 150080, China; and [d]Department of Mathematics, Harbin Institute of Technology, Harbin 150080, China

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[1]To whom correspondence may be addressed. Email: qhjiang@hit.edu.cn or jinsl@hit.edu.cn.

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Table 1. Association between rs17185536 and gene expression in 12 human tissues

Source	Tissue	Gene	EA	NEA	Beta*	SE	P value[†]
NephQTL	Glomerulus	ASCC3	T	C	0.084	0.088	3.42E-01
NephQTL	Glomerulus	MCHR2	T	C	−0.081	0.145	5.79E-01
NephQTL	Glomerulus	MCHR2-AS1	T	C	0.027	0.139	8.48E-01
NephQTL	Glomerulus	SIM1	T	C	0.015	0.127	9.08E-01
NephQTL	Tubulointerstitium	MCHR2	T	C	−0.221	0.116	6.01E-02
NephQTL	Tubulointerstitium	MCHR2-AS1	T	C	−0.124	0.122	3.09E-01
NephQTL	Tubulointerstitium	SIM1	T	C	−0.055	0.060	3.64E-01
NephQTL	Tubulointerstitium	ASCC3	T	C	0.021	0.061	7.30E-01
GTEx	Small intestine, terminal ileum	SIM1	T	C	0.016	0.150	9.14E-01
GTEx	Testis	SIM1	T	C	0.026	0.067	7.00E-01
GTEx	Skin, not sun-exposed suprapubic	SIM1	T	C	0.065	0.074	3.82E-01
GTEx	Pancreas	SIM1	T	C	−0.009	0.085	9.12E-01
GTEx	Cells, transformed fibroblasts	SIM1	T	C	0.108	0.044	1.61E-02
GTEx	Breast, mammary tissue	SIM1	T	C	0.054	0.069	4.35E-01
GTEx	Muscle, skeletal	SIM1	T	C	−0.107	0.061	7.94E-02
GTEx	Brain, hypothalamus	SIM1	T	C	0.386	0.109	6.69E-04
GTEx	Skin, sun-exposed lower leg	SIM1	T	C	0.047	0.040	2.47E-01
GTEx	Adipose, s.c.	SIM1	T	C	0.021	0.044	6.32E-01

The rs17185536 position is on chromosome 6, 100620931 bp (hg19). EA, effect allele; NEA, noneffect allele.
*Beta is the regression coefficient based on the effect allele. Beta > 0 and Beta < 0 mean that this effect allele regulates increased and reduced gene expression, respectively.
[†]The threshold of statistical significance for eQTLs analysis was $P < 0.05$.

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