

eTable 1. Genomic coordinates and targeted sequences for target bisulfite sequencing

Gene Name	Genomic position (GRCh37)	# of CpG	Distance to TSS	Genomic Target Sequence and Primers
<i>NPPA</i>	Chr1:11908380-11908117	9	-513 to -302	<p>TTTTGTTTGAGGTTAGAGGTTTGTTTA - forward primer</p> <p>CCCTGTCTGAGGCCAGAGGTCTGCCCACGTGGCGGATGAGGCAGGTGTGAGGCCA GCTTGAGCATCTGGATCCATTTGTCTCGGGCTGCTGGCTGCCTGCCATTTCTCCTC TCCACCCTTATTTGGAGGCCCTGACAGCTGAGCCACAAACAAACCAGGGGAGCTG GGCACCAGCCAAGCGTCACCCTCTGTTTCCCCGCACGGGTACCAGCGTCGAGGAG AAAGAATCCTGAGGCACGGCGGTGAGATAACCAAGGACTCTT</p> <p>AAAAATCCTTAATTATCTCACCRCC – reverse primer</p>
<i>NPPB</i>	Chr1:11919190-11918953	11	-168 to +3	<p>GGTTTATTTTTATATAAGGTYGGTTTTGTT - forward primer</p> <p>GGCCATTTCTATAACAAGGTCGGCTCTGCCCGGTCTCCACCTCCCACGTCGCAG GCGCGGAGGGGCTCATTCCCGGGCCCTGATCTCAGAGGCCCGGAATGTGGCTG ATAAATCAGAGATAACCCTGCATGGCAGGGCAGGCCCGACACTCAGCTCCAGG ATAAAAGGCCACGGTGTCCCGAGGAGCCAGGAGGAGCACCCCGCAGGCTGAG GGCAGGTGGGAAGCAAACCCGGACGC</p> <p>ACRTCCRAATTTACTTCCCACCTAC - reverse primer</p>
<i>CORIN</i>	Chr4:47840136-47839906	9	+27 to +190	<p>GGGTGGGATTTGTAGAGTAGATAA - forward primer</p> <p>GGGTGGGATCTGTAGAGCAGACAAAATATGGGGCCCCTGGCGCTTAAAGTT CAGTTTGTCTCTCTTGAGCTTGGAGAAAATCATCGTAGTGCCTCCCCGGGG GACACGTAGAGGAGAGAAAAGCGACCAAGATAAAAGTGGACAGAAGAATA AGCGGAGACTTTTTATCCATGAAACAGTCTCCTGCCCTCGCTCCGGAAGAGCG CTGCCGCAGAGCCGGGTCCCCAAAGC</p> <p>ACTTTAAAAACCCRACTCTACRACAA - reverse primer</p>

<i>FURIN</i>	Chr15:914 15936- 91416189	7	+1196 to +1366	TTAGTAAATAGTGGGTAGGGATTGG - forward primer CCAGCAAATAGTGGGCAGGGACTGGGAGCGATAAATTCACGGGAGCCTCCCAGG GCTGGTAACAGGACCCCGCGTGGTGTCTCTGCTAGAGGGAGAGACTGATTGGGT GTCCGAGTGGCCCTCCCGTGGCCTGCTCTGTGGCTGTGTCAGAGCCAGACCCCC AGTGTCTGGGAAACAGCAGTCTGTCCTGGGGTGAGGCGCAATTTGAGTGGCCA GAGTGGCTCTCTGTGTCAGGAGGTTCTGGTGCTGGAGA TCTCCAACACCAAACCTCCT - reverse primer
---------------------	---------------------------------	---	-------------------	--

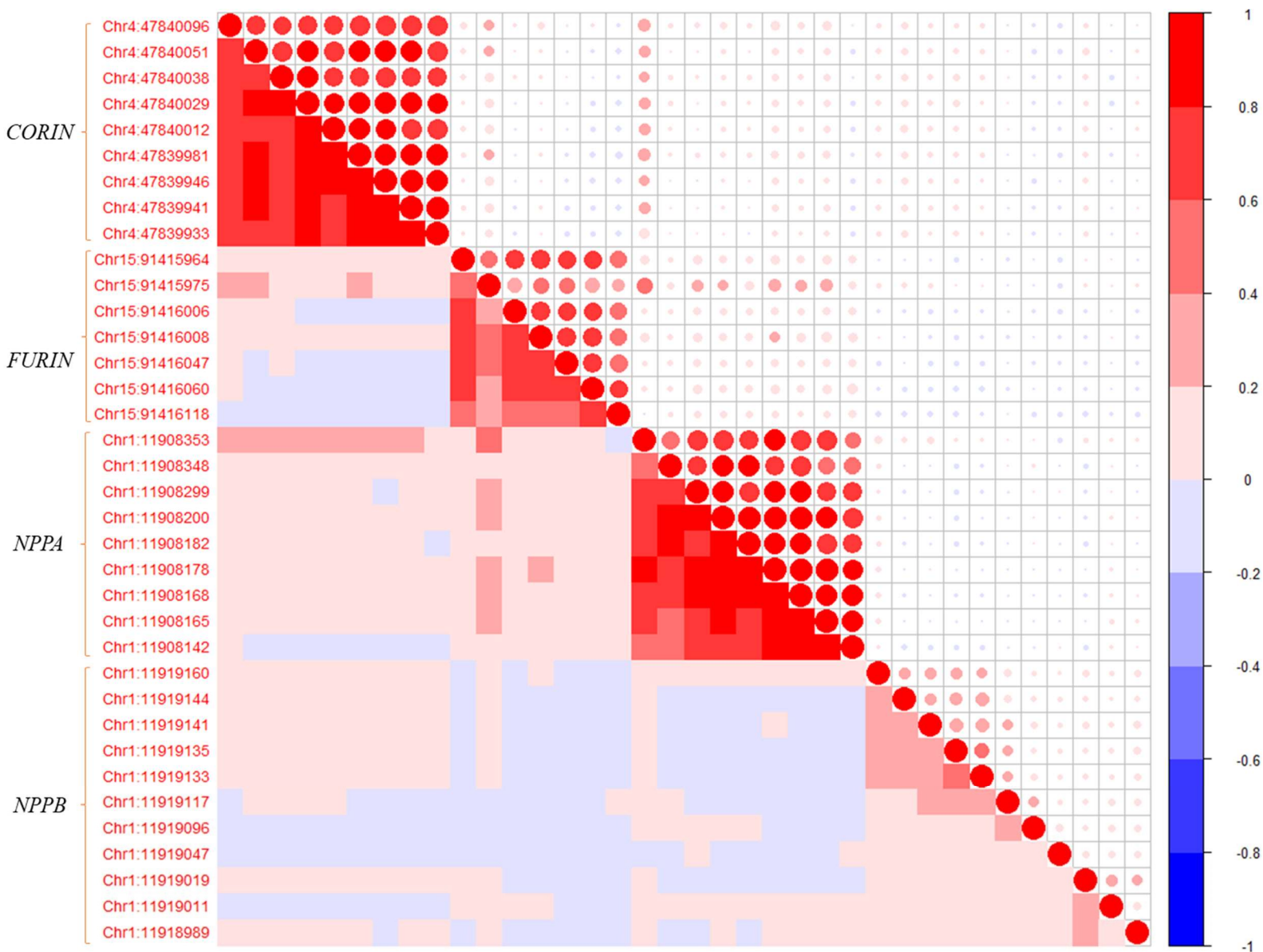
eMethods:

Demographic data including age, sex, and education level were obtained by questionnaires administered by trained staff. was classified as current smoking or not. Current smoking was defined as having smoked at least 100 cigarettes in the entire life, having smoked cigarettes regularly, and smoking currently. Alcohol consumption was classified as current drinkers or not. Current drinkers were those who had consumed any alcohol during the past year. Bodyweight (kg) and height (cm) were measured when participants wore light clothes and no shoes by trained staff. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). Blood pressure was measured three times by trained staff using a standard mercury sphygmomanometer and a cuff of appropriate size according to a standard protocol ¹, after the participants had been resting for at least 5 min in a relaxed, sitting position. The first and fifth Korotkoff sounds were recorded as systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. The mean of the three measurements was used in statistical analyses. According to the Chinese guidelines for the management of hypertension, participants with an SBP ≥ 140 mmHg and/or a DBP ≥ 90 mmHg or under antihypertensive treatment in the last 2 weeks were diagnosed with hypertension ². Fasting glucose, blood lipids including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were measured by standard laboratory methods ³. Diabetes was defined as fasting glucose ≥ 126 mg/dL (7.0 mmol/L) or self-reported history of diabetes ⁴.

eReferences:

1. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Jama* 2003;289:2560-2572.

2. Liu LS. [2010 Chinese guidelines for the management of hypertension]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2011;39:579-615.
3. Peng H, Zhang Q, Cai X, et al. Association Between High Serum Soluble Corin and Hypertension: A Cross-Sectional Study in a General Population of China. *American journal of hypertension* 2015;28:1141-1149.
4. Association AD. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. *Diabetes care* 2019;42:S13-s28.



eFigure 1. Inter-correlations among the methylation levels of the 36 CpG sites assayed

eTable 2. The single CpG associations between DNA methylation of four core NP system genes and ischemic stroke

CpG loci (GRCh37)	Relative to TSS (bp)	β (SE)	OR (95%CI)	Raw <i>P</i>	q
<i>CORIN</i>					
Chr4:47840096	27	-0.221(0.035)	0.80(0.75-0.86)	1.67E-10	1.20E-09
Chr4:47840051	72	-0.271(0.042)	0.76(0.70-0.83)	1.40E-10	1.20E-09
Chr4:47840038	85	-0.282(0.053)	0.75(0.68-0.84)	1.08E-07	3.90E-07
Chr4:47840029	94	-0.245(0.046)	0.78(0.71-0.86)	1.24E-07	4.07E-07
Chr4:47840012	111	-0.238(0.044)	0.79(0.72-0.86)	8.49E-08	3.40E-07
Chr4:47839981	142	-0.308(0.04)	0.74(0.68-0.79)	1.82E-14	2.18E-13
Chr4:47839946	177	-0.225(0.037)	0.80(0.74-0.86)	2.02E-09	1.21E-08
Chr4:47839941	182	-0.190(0.032)	0.83(0.78-0.88)	2.37E-09	1.22E-08
Chr4:47839933	190	-0.140(0.029)	0.87(0.82-0.92)	1.99E-06	5.97E-06
<i>FURIN</i>					
Chr15:91415964	1196	-0.226(0.049)	0.80(0.72-0.88)	4.19E-06	1.16E-05
Chr15:91415975	1207	-1.066(0.095)	0.34(0.29-0.41)	1.93E-29	6.94E-28
Chr15:91416006	1238	-0.092(0.051)	0.91(0.82-1.01)	7.18E-02	1.08E-01
Chr15:91416008	1240	-0.196(0.054)	0.82(0.74-0.91)	2.84E-04	6.39E-04
Chr15:91416047	1279	-0.112(0.052)	0.89(0.81-0.99)	3.15E-02	5.39E-02
Chr15:91416060	1292	-0.115(0.053)	0.89(0.80-0.99)	3.12E-02	5.39E-02
Chr15:91416118	1350	0.040(0.053)	1.04(0.94-1.15)	4.48E-01	5.37E-01
<i>NPPA</i>					
Chr1:11908353	-513	-0.592(0.067)	0.55(0.48-0.63)	5.89E-19	1.06E-17
Chr1:11908348	-508	-0.253(0.121)	0.78(0.61-0.98)	3.68E-02	6.02E-02
Chr1:11908299	-459	-0.361(0.082)	0.70(0.59-0.82)	1.08E-05	2.78E-05
Chr1:11908200	-360	-0.132(0.045)	0.88(0.80-0.96)	3.08E-03	6.15E-03
Chr1:11908182	-342	-0.144(0.06)	0.87(0.77-0.97)	1.57E-02	2.98E-02
Chr1:11908178	-338	-0.293(0.052)	0.75(0.67-0.82)	1.45E-08	6.54E-08
Chr1:11908168	-328	-0.154(0.046)	0.86(0.78-0.94)	8.14E-04	1.72E-03
Chr1:11908165	-325	-0.175(0.048)	0.84(0.76-0.92)	2.36E-04	5.65E-04
Chr1:11908142	-302	0.028(0.038)	1.03(0.95-1.11)	4.73E-01	5.49E-01
<i>NPPB</i>					
Chr1:11919160	-168	-0.047(0.031)	0.95(0.90-1.01)	1.36E-01	1.81E-01
Chr1:11919144	-152	-0.033(0.031)	0.97(0.91-1.03)	2.85E-01	3.66E-01
Chr1:11919141	-149	-0.006(0.032)	0.99(0.93-1.06)	8.60E-01	8.85E-01
Chr1:11919135	-143	0.020(0.030)	1.02(0.96-1.08)	4.93E-01	5.55E-01
Chr1:11919133	-141	0.004(0.030)	1.00(0.95-1.06)	9.05E-01	9.05E-01
Chr1:11919117	-125	-0.026(0.026)	0.97(0.93-1.03)	3.29E-01	4.08E-01

Chr1:11919096	-104	-0.006(0.026)	0.99(0.95-1.05)	8.21E-01	8.70E-01
Chr1:11919047	-55	0.067(0.042)	1.07(0.98-1.16)	1.16E-01	1.60E-01
Chr1:11919019	-27	-0.086(0.054)	0.92(0.82-1.02)	1.11E-01	1.60E-01
Chr1:11919011	-19	-0.025(0.048)	0.98(0.89-1.07)	6.02E-01	6.57E-01
Chr1:11918989	3	-0.049(0.027)	0.95(0.90-1.00)	6.65E-02	1.04E-01
