***Supplementary Material***

**DNA methylation mediate the genetic variants on platelet function recovery after ticagrelor discontinues**

## Supplementary Methods

**1.1 Sample preparation for LC-MS/MS analysis**

The plasma samples were thawed at room temperature (RT) before being subjected to extraction. An aliquot of plasma (200 µL) was combined with ferulic acid working solution (10 µg/mL, 5 µL), extracted with ethyl acetate (1.3 mL) and vortex-mixed for 5 min at RT. The sample was centrifuged at 6000 rpm for 10 min at 4°C, and an aliquot (1 mL) of the supernatant was evaporated to dryness under vacuum at ambient temperature. The residue was reconstituted in 50% water/acetonitrile (100 µL). The mixture was vortexed for 3 min at RT, followed by centrifugation at 12,000 rpm for 15 min at 4°C. An aliquot (5 µL) of the supernatant was analyzed by LC-MS/MS.

**1.2 Determination of ticagrelor and its metabolites concentrations**

A high-performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) assay was developed and validated for simultaneous determination of ticagrelor and its metabolites in human plasma. The system consisted of a prominence LC-20AB integrated system (Shimadzu, Kyoto, Japan) and an API 4000 QTrap mass spectrometer (AB Sciex, Redwood City, CA, USA) equipped with an electrospray ionization unit.

Chromatographic separation was achieved on an Ultimate XB-C18 column (2.1 mm × 150mm, 3µm) (Welch Materials Inc., Maryland, USA) at ambient temperature. The mobile phase consisted of aqueous ammonium acetate solution (0.025 mM) and acetonitrile (35:65, *v*: *v*) at a flow rate of 0.25 mL/min. The injection volume was 5 µL and the analytical run time was 4.5 min. Declustering potential (DP), entrance potential (EP), and collision energy (CE) were adjusted to give maximum sensitivity in negative ionization mode, respectively. Data acquisition was processed using Analyst 1.4.2 software (AB Sciex). Optimal mass spectrometry parameters for ticagrelor, M8 and internal standard (IS, ferulic acid) are shown in the Table below.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | ***m/z* (M-H)-** | **DP** (V) | **EP** (V) | **CE** (V) | **Retention time** (min) |
| Ticagrelor | 521.2→361.2 | -140 | -9 | -32 | 3.50 |
| M8 | 477.2→361.1 | -130 | -9 | -30 | 3.41 |
| IS  | 193.0→133.7 | -56 | -10 | -23 | 1.64 |

**1.3 Platelet function testing**Basic population pharmacodynamics (PPD) was applied to evaluate the antiplatelet effects of ticagrelor. For platelet function tests, whole blood samples (2 × 2 mL) were collected with BD Vacutainer sodium citrate tubes (1:9) at the following time points (number of volunteers): 0.5 (22), 1 (25), 2 (47), 4 (16), 8 (15) and 24 h (16) and 2 (16), 3 (14), 3.29 (1), 5 (16), 6 (5), 7 (23), 7.04 (1), 9 (4), 10 (3), 11 (4), 23 (3), and 24 days (3) after administration. ADP-stimulated platelet aggregation (PA) as measured within 2 h of sampling through light transmittance aggregometry with 20 µmol/L ADP as an agonist on Chronolog PA Systems (Vastec Medical. Ltd.). The PA post-dose until recovery to the baseline was expressed in percentage. A decentralized sampling design was used in platelet function testing. Thus, the missing PA data were imputed through Bayesian simulation. First, the data on the maximal drug effect to full recovery to the baseline PA were included in model development. The independent variable of the recovery model of PA was time, considering that antiplatelet effects were slightly related to drug concentration. A sigmoid maximal effect model (Equation 1) was used to fit the observed PA data and simulate the missing ones by using NONMEM 7.2.0 (Icon Development Solutions, Ellicott City, MD, USA).
 PA = Emax + Rmax·tγ/(RTγ 50 + tγ) (1)
where Emax is the maximum drug effect, Rmax is the maximal recovery of PA, RT50 is the time to recover 50% of the maximum drug effect, γ is the sigmoidicity or shape factor, and t is time in hours. Second, 1,000 simulations were performed based on the sigmoid model, and the missing data were imputed with the simulated median at each time point by using R (version 3.2.4). RT50 and recovery day to the baseline PA (RECDAY) were set to represent the recovery of platelet effect. RECDAY was defined as the time to recover to the baseline PA in days in accordance with the standard from the clinical laboratory of our hospital (ADP-induced PA = 69%).

## 2．Supplementary Figures



Figure S1. GWAS analysis result of RT50. (A) Manhattan plots for the suggestively associations of SNPs with RT50. The black dashed line indicates the threshold significance on RT50 (P < 0.00001). (B) QQ plots for the genome-wide p-values of RT50. The red points indicate the significant SNPs and the blue points indicates the insignificant SNPs (P < 0.00001).

1. **Supplementary Tables**

Table S1 ADME genes CpG sites that suggestively associated with M8 t1/2 (*P* < 0.05).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **CpG** | **CHR** | **MAPINFO** | **Gene** | **Region** | **Class** | **CpG\_info** | **Enhancer** | **DHS** | **Open\_chr** | **TFBS** | **BETA** | **SE** | **P** |
| cg05300248 | 18 | 24537063 | CHST9 | Body | Phase II |  | TRUE | TRUE |  |  | -88.48  | 22.22  | 0.00032 |
| cg04981696 | 16 | 16044519 | ABCC1 | Body | Transporter | S\_Shore |  | TRUE |  |  | 60.57  | 15.70  | 0.00046 |
| cg22827685 | 12 | 117768981 | NOS1 | 5'UTR | Phase I |  |  |  |  |  | -124.65  | 34.63  | 0.001 |
| cg23916679 | 4 | 70346347 | UGT2B4 | 3'UTR | Phase II |  |  |  |  |  | -64.78  | 19.08  | 0.0017 |
| cg08933008 | 9 | 86955777 | SLC28A3 | TSS200 | Transporter |  |  | TRUE |  |  | -68.16  | 20.58  | 0.0021 |
| cg02951261 | 4 | 106729052 | GSTCD | Body | Phase II |  |  |  |  | TRUE | 30.69  | 9.30  | 0.0022 |
| cg11372881 | 6 | 160807779 | SLC22A3 | Body | Transporter |  |  |  | TRUE | TRUE | -125.85  | 38.28  | 0.0023 |
| cg14204559 | 7 | 75596021 | POR | Body | Modifier |  |  | TRUE |  |  | -94.92  | 28.94  | 0.0023 |
| cg25290633 | 10 | 101601462 | ABCC2 | Body | Transporter | S\_Shore |  |  |  |  | 34.92  | 10.84  | 0.0027 |
| cg02279452 | 1 | 225996974 | EPHX1 | TSS1500 | Phase I | N\_Shore |  | TRUE |  |  | 64.39  | 20.49  | 0.0033 |
| cg00487989 | 16 | 89688244 | DPEP1 | 5'UTR | Phase I |  |  |  | TRUE |  | -79.31  | 25.29  | 0.0034 |
| cg10382845 | 16 | 48221573 | ABCC11 | Body | Transporter |  |  |  |  |  | -65.96  | 21.85  | 0.0046 |
| cg07021906 | 16 | 87866833 | SLC7A5 | Body | Transporter |  |  | TRUE |  |  | 94.93  | 32.69  | 0.0063 |
| cg15183092 | 7 | 150710447 | NOS3 | 3'UTR | Phase I | Island |  | TRUE |  |  | -88.91  | 30.79  | 0.0065 |
| cg21895884 | 11 | 64358075 | SLC22A12 | TSS1500 | Transporter |  |  | TRUE |  |  | -119.02  | 42.07  | 0.0076 |
| cg12610030 | 5 | 131723004 | SLC22A5 | Body | Transporter |  | TRUE |  | TRUE | TRUE | -80.78  | 28.63  | 0.0077 |
| cg14297374 | 22 | 46621405 | PPARA | Body | Modifier |  |  |  | TRUE | TRUE | -81.84  | 29.02  | 0.0078 |
| cg04018315 | 7 | 150710242 | NOS3 | 3'UTR | Phase I | N\_Shore |  | TRUE |  |  | -83.58  | 30.08  | 0.0086 |
| cg07556134 | 3 | 12330263 | PPARG | 5'UTR | Modifier | Island |  | TRUE |  |  | 49.37  | 17.81  | 0.0088 |
| cg00846580 | 14 | 60632234 | DHRS7 | TSS200 | Phase I | Island |  | TRUE |  |  | 42.04  | 15.20  | 0.0089 |
| cg12838928 | 16 | 16112597 | ABCC1 | Body | Transporter |  |  | TRUE |  |  | -136.77  | 49.57  | 0.0091 |
| cg16684958 | 7 | 75615977 | POR | 3'UTR | Modifier |  |  | TRUE |  |  | 104.39  | 38.03  | 0.0094 |
| cg25517015 | 19 | 17584020 | SLC27A1 | Body | Transporter | S\_Shelf |  | TRUE |  |  | -61.81  | 22.76  | 0.01 |
| cg27372063 | 7 | 75601901 | POR | Body | Modifier |  |  | TRUE |  |  | -108.23  | 40.08  | 0.01 |
| cg01083689 | 1 | 12678206 | DHRS3 | TSS1500 | Phase I | Island |  | TRUE |  |  | 22.14  | 8.23  | 0.011 |
| cg06857304 | 10 | 94826314 | CYP26C1 | Body | Phase I | Island |  |  | TRUE | TRUE | -93.00  | 34.67  | 0.011 |
| cg23796578 | 17 | 9694472 | DHRS7C | 1stExon | Phase I |  |  |  |  |  | -84.95  | 31.70  | 0.011 |
| cg03469471 | 7 | 150707830 | NOS3 | Body | Phase I | S\_Shore |  | TRUE |  |  | 81.06  | 30.27  | 0.011 |
| cg03010425 | 11 | 2944771 | SLC22A18 | Body | Transporter | S\_Shore |  | TRUE |  |  | -63.57  | 23.79  | 0.011 |
| cg13612480 | 19 | 1103771 | GPX4 | TSS1500 | Phase I | Island |  |  | TRUE | TRUE | 45.82  | 17.16  | 0.011 |
| cg02489968 | 11 | 45674238 | CHST1 | 5'UTR | Phase II | S\_Shore |  |  | TRUE |  | -56.25  | 21.17  | 0.012 |
| cg20955839 | 2 | 108922813 | SULT1C2 | Body | Phase II |  |  |  |  |  | -71.23  | 26.85  | 0.012 |
| cg17347634 | 8 | 65711916 | CYP7B1 | TSS1500 | Phase I | S\_Shore |  | TRUE |  |  | 48.92  | 18.47  | 0.012 |
| cg07013799 | 11 | 17409188 | KCNJ11 | 1stExon | Modifier | N\_Shore |  |  |  | TRUE | -85.75  | 32.45  | 0.012 |
| cg19836718 | 11 | 17464823 | ABCC8 | Body | Transporter |  |  |  |  |  | -87.98  | 33.31  | 0.012 |
| cg21201924 | 9 | 137251825 | RXRA | Body | Modifier | N\_Shore |  |  | TRUE |  | -68.29  | 26.05  | 0.013 |
| cg01714149 | 5 | 101834362 | SLCO6A1 | 1stExon | Transporter | Island |  |  |  | TRUE | -53.09  | 20.25  | 0.013 |
| cg13594863 | 11 | 17496264 | ABCC8 | Body | Transporter | N\_Shore |  | TRUE |  |  | -85.70  | 32.69  | 0.013 |
| cg08691490 | 17 | 48735420 | ABCC3 | Body | Transporter |  |  | TRUE |  |  | -123.56  | 47.24  | 0.013 |
| cg11907090 | 3 | 14459570 | SLC6A6 | 5'UTR | Transporter |  |  |  |  | TRUE | -65.00  | 24.91  | 0.013 |
| cg11844800 | 1 | 19201860 | ALDH4A1 | Body | Phase I | N\_Shelf |  | TRUE |  |  | -127.18  | 48.85  | 0.013 |
| cg05640674 | 5 | 131722561 | SLC22A5 | Body | Transporter |  |  | TRUE |  |  | -61.26  | 23.55  | 0.013 |
| cg21748751 | 6 | 35309867 | PPARD | TSS1500 | Modifier | N\_Shore |  |  | TRUE | TRUE | -93.23  | 36.18  | 0.014 |
| cg07040598 | 11 | 17435702 | ABCC8 | Body | Transporter |  |  |  | TRUE |  | -82.03  | 31.89  | 0.014 |
| cg15646911 | 17 | 19551890 | ALDH3A2 | TSS200 | Phase I | Island |  | TRUE |  |  | 81.44  | 31.76  | 0.015 |
| cg03860210 | 19 | 41619386 | CYP2F1 | TSS1500 | Phase I |  |  |  |  |  | -62.51  | 24.43  | 0.015 |
| cg13466809 | 6 | 160542944 | SLC22A1 | 1stExon | Transporter |  |  | TRUE |  |  | -86.33  | 33.76  | 0.015 |
| cg21979196 | 8 | 70745736 | SLCO5A1 | 5'UTR | Transporter | Island |  | TRUE |  |  | 34.27  | 13.44  | 0.015 |
| cg20372755 | 14 | 23616151 | SLC7A8 | 5'UTR | Transporter |  |  |  | TRUE | TRUE | -86.37  | 33.93  | 0.015 |
| cg20112357 | 2 | 169925953 | DHRS9 | ExonBnd | Phase I |  |  | TRUE |  |  | 69.36  | 27.25  | 0.015 |
| cg12975461 | 11 | 2937847 | SLC22A18 | ExonBnd | Transporter |  |  | TRUE |  |  | -64.22  | 25.31  | 0.016 |
| cg06236276 | 6 | 160680078 | SLC22A2 | TSS200 | Transporter | S\_Shore |  | TRUE |  |  | -86.38  | 34.18  | 0.016 |
| cg12969918 | 19 | 34249189 | CHST8 | Body | Phase II |  |  | TRUE |  |  | -61.46  | 24.35  | 0.016 |
| cg05706446 | 11 | 74863001 | SLCO2B1 | Body | Transporter |  |  | TRUE |  |  | -66.09  | 26.32  | 0.017 |
| cg17112266 | 7 | 150737198 | ABCB8 | Body | Transporter | N\_Shelf |  | TRUE |  |  | -156.58  | 62.48  | 0.017 |
| cg04069642 | 15 | 75016096 | CYP1A1 | 5'UTR | Phase I | N\_Shelf |  |  | TRUE | TRUE | -34.91  | 13.93  | 0.017 |
| cg18827685 | 7 | 75614882 | POR | ExonBnd | Modifier |  |  | TRUE |  |  | -55.41  | 22.18  | 0.017 |
| cg03296424 | 17 | 19646818 | ALDH3A1 | Body | Phase I | N\_Shore |  | TRUE |  |  | -80.35  | 32.17  | 0.017 |
| cg20748065 | 7 | 75583421 | POR | Body | Modifier |  |  | TRUE |  |  | 35.94  | 14.40  | 0.017 |
| cg24241662 | 9 | 137297892 | RXRA | Body | Modifier | N\_Shore |  | TRUE |  |  | -103.74  | 41.74  | 0.018 |
| cg08450807 | 13 | 103702677 | SLC10A2 | Body | Transporter |  |  |  |  |  | -49.48  | 19.92  | 0.018 |
| cg19765820 | 1 | 116518738 | SLC22A15 | TSS1500 | Transporter | N\_Shore |  | TRUE |  |  | 28.27  | 11.38  | 0.018 |
| cg19659215 | 12 | 21488180 | SLCO1A2 | 5'UTR | Transporter |  |  |  |  |  | -74.87  | 30.16  | 0.018 |
| cg23168628 | 16 | 16222019 | ABCC1 | Body | Transporter |  |  |  |  | TRUE | -76.66  | 30.93  | 0.018 |
| cg13534901 | 7 | 17339481 | AHR | Body | Modifier | S\_Shore |  | TRUE |  |  | 23.96  | 9.67  | 0.018 |
| cg05964971 | 16 | 16289065 | ABCC6 | Body | Transporter |  |  |  | TRUE | TRUE | -62.34  | 25.19  | 0.018 |
| cg14542876 | 10 | 106012745 | GSTO1 | TSS1500 | Phase II | N\_Shore | TRUE |  |  | TRUE | 29.57  | 11.99  | 0.019 |
| cg04191678 | 1 | 171153458 | FMO2 | TSS1500 | Phase I |  |  |  |  |  | -51.48  | 20.90  | 0.019 |
| cg15672065 | 6 | 32805142 | TAP2 | Body | Transporter | N\_Shore |  |  |  | TRUE | 59.98  | 24.39  | 0.019 |
| cg20149948 | 3 | 183729324 | ABCC5 | Body | Transporter |  |  | TRUE |  |  | -41.16  | 16.76  | 0.019 |
| cg08919084 | 15 | 92555388 | SLCO3A1 | Body | Transporter |  | TRUE | TRUE |  |  | -43.70  | 17.80  | 0.019 |
| cg24188953 | 20 | 43021951 | HNF4A | Body | Modifier |  |  | TRUE |  |  | -126.42  | 51.71  | 0.02 |
| cg01829163 | 16 | 87871160 | SLC7A5 | Body | Transporter |  |  |  | TRUE | TRUE | 37.43  | 15.33  | 0.02 |
| cg10036402 | 14 | 77787255 | GSTZ1 | TSS200 | Phase II | Island |  | TRUE |  |  | 151.01  | 61.86  | 0.02 |
| cg24293126 | 1 | 9127841 | SLC2A5 | Body | Transporter | N\_Shelf |  |  | TRUE | TRUE | -47.90  | 19.79  | 0.021 |
| cg17498845 | 8 | 70468513 | SULF1 | 5'UTR | Phase I |  |  |  | TRUE | TRUE | -37.15  | 15.42  | 0.021 |
| cg26919154 | 7 | 17339044 | AHR | Body | Modifier | Island |  | TRUE |  |  | 41.72  | 17.41  | 0.022 |
| cg19627213 | 6 | 160679974 | SLC22A2 | TSS200 | Transporter | S\_Shore |  | TRUE |  |  | -71.13  | 29.74  | 0.022 |
| cg27586378 | 19 | 49063066 | SULT2B1 | Body | Phase II | S\_Shore |  | TRUE |  |  | -96.37  | 40.38  | 0.022 |
| cg03892693 | 11 | 2937098 | SLC22A18 | Body | Transporter |  |  | TRUE |  |  | -83.47  | 34.99  | 0.022 |
| cg26229274 | 5 | 131629510 | SLC22A4 | TSS1500 | Transporter | Island |  | TRUE |  |  | 46.45  | 19.50  | 0.023 |
| cg25411725 | 3 | 38306672 | SLC22A13 | TSS1500 | Transporter |  |  |  |  |  | -53.53  | 22.58  | 0.023 |
| cg15266969 | 11 | 64369352 | SLC22A12 | 3'UTR | Transporter |  |  |  | TRUE |  | -56.29  | 23.86  | 0.024 |
| cg01510388 | 8 | 65711658 | CYP7B1 | TSS1500 | Phase I | Island |  | TRUE |  |  | 48.88  | 20.76  | 0.024 |
| cg19304891 | 7 | 117205433 | CFTR | Body | Modifier |  |  |  |  |  | 46.76  | 19.95  | 0.025 |
| cg09749867 | 6 | 160640676 | SLC22A2 | Body | Transporter |  |  |  |  |  | -82.55  | 35.23  | 0.025 |
| cg05691848 | 22 | 46610981 | PPARA | Body | Modifier | S\_Shore |  |  |  |  | -45.04  | 19.22  | 0.025 |
| cg02064674 | 8 | 70690124 | SLCO5A1 | Body | Transporter |  |  | TRUE |  |  | 40.41  | 17.26  | 0.025 |
| cg08363693 | 19 | 49063796 | SULT2B1 | Body | Phase II | S\_Shelf |  |  | TRUE | TRUE | -59.29  | 25.33  | 0.025 |
| cg27518648 | 21 | 43671075 | ABCG1 | Body | Transporter |  |  | TRUE |  |  | -146.45  | 62.81  | 0.025 |
| cg14778875 | 8 | 70461961 | SULF1 | 5'UTR | Phase I |  | TRUE |  |  |  | -50.73  | 21.77  | 0.026 |
| cg05050460 | 19 | 34132840 | CHST8 | 5'UTR | Phase II |  |  | TRUE |  |  | -64.93  | 27.92  | 0.026 |
| cg15579148 | 7 | 95064694 | PON2 | TSS1500 | Phase I | S\_Shore |  | TRUE |  |  | -36.68  | 15.78  | 0.026 |
| cg07250080 | 6 | 32822278 | TAP1 | Body | Transporter | Island |  | TRUE |  |  | -52.09  | 22.41  | 0.026 |
| cg00700487 | 7 | 150706128 | NOS3 | Body | Phase I | Island |  |  | TRUE | TRUE | -41.11  | 17.71  | 0.026 |
| cg24823791 | 4 | 106631232 | GSTCD | 5'UTR | Phase II | S\_Shore |  |  |  | TRUE | 21.04  | 9.06  | 0.026 |
| cg11926430 | 1 | 209883607 | HSD11B1 | Body | Phase I |  |  | TRUE |  |  | -78.19  | 33.71  | 0.026 |
| cg20285745 | 12 | 117798627 | NOS1 | 5'UTR | Phase I | Island |  | TRUE |  |  | -25.75  | 11.10  | 0.026 |
| cg24677278 | 6 | 28479430 | GPX6 | Body | Phase I |  |  | TRUE |  |  | -52.27  | 22.55  | 0.026 |
| cg10410932 | 7 | 117208084 | CFTR | Body | Modifier |  |  | TRUE |  |  | -89.74  | 38.75  | 0.026 |
| cg13925776 | 3 | 119531559 | NR1I2 | Body | Modifier | S\_Shelf |  | TRUE |  |  | -57.50  | 24.91  | 0.027 |
| cg06522879 | 11 | 64358276 | SLC22A12 | TSS200 | Transporter |  |  |  | TRUE |  | -50.04  | 21.70  | 0.027 |
| cg01794926 | 15 | 92470387 | SLCO3A1 | Body | Transporter |  | TRUE | TRUE |  |  | -56.67  | 24.63  | 0.027 |
| cg24718773 | 2 | 138739074 | HNMT | Body | Phase II |  |  | TRUE |  |  | 63.65  | 27.70  | 0.028 |
| cg27659071 | 6 | 52859607 | GSTA4 | 5'UTR | Phase II | Island |  | TRUE |  |  | -23.77  | 10.37  | 0.028 |
| cg12931707 | 4 | 115527443 | UGT8 | 5'UTR | Phase II |  | TRUE |  |  |  | -59.82  | 26.10  | 0.028 |
| cg09441702 | 8 | 70746387 | SLCO5A1 | 5'UTR | Transporter | Island |  | TRUE |  |  | 36.84  | 16.14  | 0.028 |
| cg10122855 | 11 | 14795513 | PDE3B | Body | Phase I |  | TRUE | TRUE |  |  | -30.21  | 13.27  | 0.029 |
| cg19833985 | 1 | 53067944 | GPX7 | TSS200 | Phase I | Island |  | TRUE |  |  | 55.08  | 24.24  | 0.029 |
| cg09239591 | 2 | 31638511 | XDH | TSS1500 | Phase I |  |  | TRUE |  |  | -92.48  | 40.78  | 0.029 |
| cg19257089 | 19 | 34264089 | CHST8 | 3'UTR | Phase II | S\_Shore |  |  |  |  | -46.20  | 20.39  | 0.03 |
| cg06841499 | 11 | 67349641 | GSTP1 | TSS1500 | Phase II | N\_Shore |  | TRUE |  |  | -60.99  | 26.94  | 0.03 |
| cg13866093 | 6 | 28502727 | GPX5 | 3'UTR | Phase I |  |  |  |  |  | -36.88  | 16.30  | 0.03 |
| cg25471404 | 6 | 43395120 | ABCC10 | TSS200 | Transporter | N\_Shore |  | TRUE |  |  | 34.64  | 15.32  | 0.03 |
| cg02314896 | 19 | 49059802 | SULT2B1 | Body | Phase II | N\_Shore |  | TRUE |  |  | -53.19  | 23.56  | 0.03 |
| cg01611665 | 19 | 17581121 | SLC27A1 | TSS200 | Transporter | N\_Shore |  | TRUE |  |  | 29.69  | 13.23  | 0.031 |
| cg08482829 | 10 | 73724746 | CHST3 | 5'UTR | Phase II | Island |  | TRUE |  |  | -48.55  | 21.64  | 0.031 |
| cg12588047 | 9 | 86956573 | SLC28A3 | TSS1500 | Transporter |  |  |  |  |  | -34.25  | 15.29  | 0.031 |
| cg16680018 | 1 | 165667870 | ALDH9A1 | 1stExon | Phase I | S\_Shore |  | TRUE |  |  | 28.61  | 12.77  | 0.031 |
| cg00050375 | 6 | 43404828 | ABCC10 | Body | Transporter |  | TRUE | TRUE |  |  | -42.28  | 18.90  | 0.032 |
| cg14545975 | 9 | 137297213 | RXRA | Body | Modifier | N\_Shore | TRUE | TRUE |  |  | -88.70  | 39.67  | 0.032 |
| cg22588692 | 19 | 34195071 | CHST8 | Body | Phase II |  |  | TRUE |  |  | -69.77  | 31.22  | 0.032 |
| cg26104981 | 16 | 16247320 | ABCC6 | Body | Transporter |  |  |  |  | TRUE | -78.95  | 35.35  | 0.032 |
| cg25524784 | 6 | 32820893 | TAP1 | TSS1500 | Transporter | Island |  | TRUE |  |  | 31.20  | 13.97  | 0.032 |
| cg00167916 | 6 | 32795877 | TAP2 | 3'UTR | Transporter |  |  |  |  |  | -38.75  | 17.37  | 0.032 |
| cg16400025 | 22 | 43045209 | CYB5R3 | Body | Phase I | Island |  | TRUE |  |  | 32.12  | 14.41  | 0.032 |
| cg19403973 | 17 | 19563573 | ALDH3A2 | Body | Phase I |  |  |  |  | TRUE | 30.83  | 13.84  | 0.032 |
| cg24407350 | 19 | 34211778 | CHST8 | Body | Phase II |  |  |  | TRUE | TRUE | -80.12  | 36.01  | 0.032 |
| cg21536925 | 5 | 150399422 | GPX3 | TSS1500 | Phase I | N\_Shore |  |  |  | TRUE | 56.61  | 25.56  | 0.033 |
| cg14228987 | 16 | 75569749 | CHST5 | TSS1500 | Phase II |  |  | TRUE |  |  | 25.86  | 11.69  | 0.033 |
| cg01160258 | 6 | 24531111 | ALDH5A1 | Body | Phase I |  |  |  |  |  | -56.80  | 25.79  | 0.034 |
| cg12581549 | 19 | 34264076 | CHST8 | 3'UTR | Phase II | S\_Shore |  |  |  |  | -76.82  | 34.90  | 0.034 |
| cg08830485 | 11 | 17410707 | KCNJ11 | 5'UTR | Modifier | Island |  | TRUE |  |  | 67.12  | 30.50  | 0.034 |
| cg04903060 | 1 | 110282995 | GSTM3 | 5'UTR | Phase II | Island | TRUE | TRUE |  |  | 45.06  | 20.51  | 0.035 |
| cg10775893 | 9 | 107690540 | ABCA1 | TSS200 | Transporter | Island |  | TRUE |  |  | 33.49  | 15.25  | 0.035 |
| cg10937867 | 4 | 70613539 | SULT1B1 | Body | Phase II |  |  | TRUE |  |  | -39.73  | 18.11  | 0.035 |
| cg22467052 | 7 | 117307076 | CFTR | Body | Modifier |  | TRUE |  |  |  | -43.83  | 19.99  | 0.035 |
| cg01117627 | 14 | 100150713 | CYP46A1 | TSS200 | Phase I | Island |  |  | TRUE | TRUE | -92.47  | 42.22  | 0.035 |
| cg16719517 | 21 | 37442385 | CBR1 | 1stExon | Phase I | Island |  | TRUE |  |  | 37.45  | 17.12  | 0.035 |
| cg10887937 | 12 | 112203795 | ALDH2 | TSS1500 | Phase I | N\_Shore |  |  |  | TRUE | 39.62  | 18.18  | 0.036 |
| cg19604369 | 10 | 101604657 | ABCC2 | Body | Transporter |  |  |  |  |  | 28.70  | 13.17  | 0.036 |
| cg08407434 | 20 | 43001691 | HNF4A | Body | Modifier |  |  |  |  |  | 30.75  | 14.12  | 0.036 |
| cg12438215 | 11 | 67441397 | ALDH3B2 | 5'UTR | Phase I |  |  |  |  |  | -86.23  | 39.60  | 0.036 |
| cg04614700 | 14 | 23816109 | SLC22A17 | Body | Transporter | Island |  | TRUE |  |  | -55.66  | 25.59  | 0.036 |
| cg26623266 | 17 | 48745283 | ABCC3 | 3'UTR | Transporter |  |  |  | TRUE | TRUE | -51.45  | 23.68  | 0.036 |
| cg11012835 | 6 | 32821289 | TAP1 | TSS1500 | Transporter | Island |  |  | TRUE | TRUE | 36.46  | 16.80  | 0.037 |
| cg20603630 | 16 | 48214922 | ABCC11 | Body | Transporter |  |  | TRUE |  |  | -71.56  | 32.97  | 0.037 |
| cg08088381 | 15 | 85457793 | SLC28A1 | Body | Transporter |  |  |  |  | TRUE | -39.75  | 18.33  | 0.037 |
| cg10700299 | 4 | 100243181 | ADH1B | TSS1500 | Phase I |  |  |  |  |  | -48.62  | 22.45  | 0.037 |
| cg14449910 | 11 | 2919689 | SLC22A18AS | Body | Transporter | N\_Shelf | TRUE |  | TRUE | TRUE | -84.22  | 38.89  | 0.037 |
| cg14449910 | 11 | 2919689 | SLC22A18AS | Body | Transporter | N\_Shelf | TRUE |  | TRUE | TRUE | -84.22  | 38.89  | 0.037 |
| cg04579507 | 12 | 21324585 | SLCO1B1 | Body | Transporter |  |  |  |  |  | -41.52  | 19.20  | 0.037 |
| cg20464948 | 15 | 92634590 | SLCO3A1 | Body | Transporter |  | TRUE | TRUE |  |  | -84.14  | 38.92  | 0.037 |
| cg05939495 | 15 | 74660110 | CYP11A1 | TSS200 | Phase I | S\_Shore |  | TRUE |  |  | -93.33  | 43.20  | 0.037 |
| cg14678167 | 13 | 52510257 | ATP7B | Body | Modifier |  |  | TRUE |  |  | -59.22  | 27.42  | 0.038 |
| cg07677296 | 16 | 1877182 | HAGH | 5'UTR | Phase I | Island |  | TRUE |  |  | 63.00  | 29.18  | 0.038 |
| cg14719865 | 5 | 101834365 | SLCO6A1 | 1stExon | Transporter | Island |  |  |  | TRUE | -50.21  | 23.26  | 0.038 |
| cg25313204 | 6 | 160768801 | SLC22A3 | TSS1500 | Transporter | Island |  | TRUE |  |  | -39.04  | 18.17  | 0.038 |
| cg23159233 | 22 | 46571660 | PPARA | 5'UTR | Modifier |  |  | TRUE |  |  | 45.75  | 21.29  | 0.038 |
| cg24867653 | 3 | 38306594 | SLC22A13 | TSS1500 | Transporter |  |  |  |  |  | -38.64  | 18.04  | 0.039 |
| cg04348026 | 15 | 51599844 | CYP19A1 | 5'UTR | Phase I |  |  |  |  |  | 37.27  | 17.41  | 0.039 |
| cg14571125 | 6 | 32796739 | TAP2 | Body | Transporter |  |  | TRUE |  |  | 57.26  | 26.77  | 0.039 |
| cg15510895 | 19 | 34178390 | CHST8 | 5'UTR | Phase II | S\_Shelf |  | TRUE |  |  | -37.15  | 17.37  | 0.039 |
| cg08402107 | 10 | 106028939 | GSTO2 | 5'UTR | Phase II | Island |  | TRUE |  |  | 18.28  | 8.57  | 0.04 |
| cg11321922 | 1 | 161201121 | NR1I3 | ExonBnd | Modifier |  |  | TRUE |  |  | -101.52  | 47.61  | 0.04 |
| cg17610535 | 1 | 209897614 | HSD11B1 | Body | Phase I |  |  | TRUE |  |  | -92.25  | 43.31  | 0.04 |
| cg10886442 | 3 | 142838320 | CHST2 | TSS1500 | Phase II | Island |  | TRUE |  |  | 29.06  | 13.64  | 0.04 |
| cg03924715 | 3 | 126246115 | CHST13 | Body | Phase II | S\_Shelf |  | TRUE |  |  | -62.32  | 29.29  | 0.04 |
| cg09003508 | 12 | 112217647 | ALDH2 | Body | Phase I |  |  | TRUE |  |  | -63.96  | 30.09  | 0.04 |
| cg15274047 | 19 | 1102570 | GPX4 | TSS1500 | Phase I | N\_Shore |  | TRUE |  |  | -47.74  | 22.46  | 0.04 |
| cg13938211 | 10 | 106053665 | GSTO2 | Body | Phase II |  |  |  |  |  | -51.95  | 24.47  | 0.041 |
| cg24036612 | 5 | 101633158 | SLCO4C1 | TSS1500 | Transporter | S\_Shore |  |  |  |  | 25.80  | 12.18  | 0.041 |
| cg19502694 | 6 | 110725921 | DDO | Body | Phase I |  |  | TRUE |  |  | -75.34  | 35.63  | 0.041 |
| cg13921918 | 13 | 95854612 | ABCC4 | Body | Transporter |  |  | TRUE |  |  | -110.62  | 52.34  | 0.042 |
| cg23925567 | 7 | 150729818 | ABCB8 | Body | Transporter | S\_Shelf |  |  |  |  | -68.18  | 32.30  | 0.042 |
| cg05182002 | 4 | 106629115 | GSTCD | TSS1500 | Phase II | N\_Shore |  |  | TRUE | TRUE | 21.42  | 10.15  | 0.042 |
| cg13283834 | 6 | 43411069 | ABCC10 | Body | Transporter |  |  | TRUE |  |  | -80.83  | 38.39  | 0.042 |
| cg11924019 | 15 | 75019283 | CYP1A1 | TSS1500 | Phase I | Island |  | TRUE |  |  | -36.66  | 17.42  | 0.042 |
| cg20397692 | 6 | 32802598 | TAP2 | Body | Transporter | N\_Shelf |  |  |  |  | 29.19  | 13.89  | 0.043 |
| cg07734514 | 6 | 28498759 | GPX5 | Body | Phase I |  | TRUE |  |  |  | -49.81  | 23.79  | 0.043 |
| cg13505691 | 21 | 43665609 | ABCG1 | Body | Transporter |  | TRUE | TRUE |  |  | -32.36  | 15.46  | 0.043 |
| cg04157431 | 3 | 119501187 | NR1I2 | TSS1500 | Modifier |  |  |  |  |  | -32.70  | 15.67  | 0.044 |
| cg04780684 | 19 | 34262555 | CHST8 | Body | Phase II | N\_Shore |  | TRUE |  |  | 58.98  | 28.30  | 0.044 |
| cg14464741 | 22 | 46620592 | PPARA | Body | Modifier |  |  | TRUE |  |  | -77.77  | 37.32  | 0.044 |
| cg16535298 | 4 | 70518959 | UGT2A1 | 1stExon | Phase II |  |  |  |  |  | -25.89  | 12.44  | 0.045 |
| cg01453929 | 1 | 113498928 | SLC16A1 | 1stExon | Transporter | Island |  | TRUE |  |  | -13.19  | 6.34  | 0.045 |
| cg04880968 | 6 | 28501879 | GPX5 | Body | Phase I |  |  |  |  |  | 22.80  | 10.97  | 0.045 |
| cg17599998 | 13 | 99403634 | SLC15A1 | Body | Transporter | N\_Shore |  | TRUE |  |  | -28.46  | 13.69  | 0.045 |
| cg06930722 | 12 | 105114327 | CHST11 | Body | Phase II |  |  | TRUE |  |  | 30.06  | 14.49  | 0.045 |
| cg09325679 | 19 | 17597534 | SLC27A1 | Body | Transporter | Island |  |  |  |  | 45.48  | 21.98  | 0.046 |
| cg09422301 | 6 | 24494043 | ALDH5A1 | TSS1500 | Phase I | N\_Shore |  |  | TRUE | TRUE | -29.91  | 14.46  | 0.046 |
| cg03862582 | 14 | 74551639 | ALDH6A1 | TSS1500 | Phase I | Island |  | TRUE |  |  | 39.82  | 19.25  | 0.046 |
| cg17809632 | 2 | 27435717 | SLC5A6 | TSS1500 | Transporter | Island |  | TRUE |  |  | 33.94  | 16.42  | 0.046 |
| cg05275649 | 12 | 21483871 | SLCO1A2 | Body | Transporter |  |  | TRUE |  |  | -54.44  | 26.38  | 0.046 |
| cg10118456 | 16 | 16065831 | ABCC1 | Body | Transporter |  | TRUE |  |  | TRUE | -45.91  | 22.28  | 0.047 |
| cg04451134 | 12 | 20723885 | PDE3A | TSS1500 | Phase I |  |  |  |  |  | -35.29  | 17.15  | 0.047 |
| cg16360659 | 6 | 28484320 | GPX6 | TSS1500 | Phase I |  |  |  |  |  | -27.76  | 13.49  | 0.047 |
| cg14871333 | 11 | 67777770 | ALDH3B1 | TSS200 | Phase I |  | TRUE | TRUE |  |  | -44.82  | 21.82  | 0.047 |
| cg17935811 | 1 | 12678641 | DHRS3 | TSS1500 | Phase I | Island |  | TRUE |  |  | 46.75  | 22.77  | 0.047 |
| cg14265066 | 9 | 137326227 | RXRA | Body | Modifier |  |  |  | TRUE |  | 37.27  | 18.17  | 0.048 |
| cg10272922 | 13 | 95673005 | ABCC4 | 3'UTR | Transporter |  |  | TRUE |  |  | -32.03  | 15.62  | 0.048 |
| cg25615529 | 21 | 43654863 | ABCG1 | Body | Transporter | Island |  | TRUE |  |  | 48.59  | 23.69  | 0.048 |
| cg15955341 | 1 | 110198890 | GSTM4 | Body | Phase II | Island |  | TRUE |  |  | 31.37  | 15.30  | 0.048 |
| cg04216262 | 20 | 45299651 | SLC13A3 | 5'UTR | Transporter |  |  | TRUE |  |  | 17.74  | 8.65  | 0.048 |
| cg12737452 | 13 | 52548992 | ATP7B | Body | Modifier |  |  |  |  | TRUE | -77.44  | 37.81  | 0.048 |
| cg08359775 | 9 | 137297979 | RXRA | Body | Modifier | N\_Shore |  |  | TRUE | TRUE | -61.63  | 30.10  | 0.048 |
| cg04661740 | 9 | 137257799 | RXRA | Body | Modifier |  |  | TRUE |  |  | -105.65  | 51.62  | 0.048 |
| cg01187418 | 11 | 114182997 | NNMT | Body | Phase II |  |  |  |  |  | -69.84  | 34.13  | 0.048 |
| cg11192688 | 1 | 171226702 | FMO1 | 5'UTR | Phase I |  |  | TRUE |  |  | -65.92  | 32.33  | 0.049 |
| cg13550546 | 12 | 117747991 | NOS1 | TSS1500 | Phase I |  |  |  |  |  | -68.21  | 33.46  | 0.049 |
| cg17919396 | 15 | 101440419 | ALDH1A3 | Body | Phase I |  | TRUE |  |  |  | 42.68  | 20.98  | 0.049 |
| cg07220939 | 11 | 64358617 | SLC22A12 | 1stExon | Transporter |  |  | TRUE |  |  | -47.42  | 23.34  | 0.05 |
| cg09016162 | 22 | 43037934 | CYB5R3 | TSS1500 | Phase I |  |  | TRUE |  |  | -26.96  | 13.28  | 0.05 |

MAPINFO : Chromosomal coordinates of the CpG (Build 37) ; Region: Gene region feature category describing the CpG position, from UCSC: TSS200 = 0–200 bases upstream of the transcriptional start site (TSS), TSS1500 = 200–1500 bases upstream of the TSS, 5'UTR = Within the 5' untranslated region, between the TSS and the ATG start site, Body = Between the ATG and stop codon; irrespective of the presence of introns, exons, TSS, or promoters, 3'UTR = Between the stop codon and poly A signal; Class: Phase I/II = metabolism enzymes, responsible for the modification of functional groups and the conjugation with endogenous moieties respectively, transporters = responsible for the uptake and excretion of drugs in and out of cells, modifiers = can either alter the expression of other ADME genes or affect the biochemistry of ADME enzymes; CpG\_info: The location of the CpG relative to the CpG island, Shore = 0–2 kb from island, Shelf = 2–4 kb from island, N = upstream (5’) of CpG island, S = downstream (3’) of CpG island; Enhancer: Predicted enhancer elements as annotated in the original 450K design; DHS: DNase I hypersensitivity site; Open\_chr: Open chromatin; TFBS: Transcription factor binding site; SE: Standard error; TRUE: There is evidence shows the region of CpG sites is potentially correlated to the gene regulation elements

Table S2. Correlation between interested CpG sites and their annotated genes.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| CpG | Gene | Estimate | P | Catalog |
| cg25290633 | ABCC2 | 0.10  | 0.04  | core ADME |
| cg05640674 | SLC22A5 | NA | NA | CIT |
| cg05300248 | CHST9 | -0.05  | 0.03  | CIT |
| cg00846580 | DHRS7 | -0.04  | 0.37  | CIT |
| cg06338150 | NOTCH1 | -0.054 | 0.61 | Coloc |
| cg17456097 | RPS6KA1 | 0.037  | 0.42  | Coloc |

Gene, the gene corresponding to the CpG sties annotated based on annotation file from Illumina. NA, the DNA methylation of CpG sites missing in the GSE56581 dataset; core ADME, the CpG site annotated to the gene belong to the core ADME gene list defined by the Pharmaadme website; CIT, the CpG sites pass causal inference test analysis; Coloc, the CpG sites colocalized with RT50.

Table S3. Comparison between CIT analysis result after removing 2 outliers of M8 t1/2

|  |  |  |  |
| --- | --- | --- | --- |
| **mQTL** | **CpG** | **p\_cit** | **p\_cit\_outlier** |
| rs78333049 | cg05640674 | 0.048 | 0.256 |
| rs9955805 | cg05300248 | 0.046 | 0.051 |
| rs151246 | cg05300248 | 0.032 | 0.055 |
| rs12957029 | cg05300248 | 0.032 | 0.389 |
| rs605761 | cg05300248 | 0.040 | 0.052 |
| rs11624065 | cg00846580 | 0.047 | 0.368 |

p\_cit, the omnibus p-value of CIT analysis among 46 samples; p\_cit, the omnibus p-value of CIT analysis among 44 samples after removing 2 samples with outliers.