Caffeine Therapy for Apnea of Prematurity: Role of the Circadian CLOCK Gene Polymorphism

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----Supplemental information----
Table 1 Genotyping information for 88 selected single nucleotide polymorphisms (SNPs)

| Gene | SNP-ID    | 1st-PCRP                  | 2nd-PCRP                  | Amplification length (bp) | UEP_SEQ                        |
|------|-----------|---------------------------|---------------------------|---------------------------|--------------------------------|
| AHR  | rs10249788| ACGTTGGATGTCCTGCGCCCATCTGGATT | ACGTTGGATGCTTTACGTCTCATGCTCAG | 101                       | GGCCCTCAGAGAAGA                |
| AHR  | rs10250822| ACGTTGGATGTCCTTCTTACTACCTTCTG | ACGTTGGATGACAAATGCACTACAGCAG | 98                        | GTCTACTGATACATTTAAAGTCT        |
| AHR  | rs1476080 | ACGTTGGATGCACACTATCGTCGTATCCTC | ACGTTGGATGCACACACACACAGTAC | 104                       | ggacGCAAGACCCCTACCTGGTGTATC   |
| AHR  | rs2066853 | ACGTTGGATGCTCTGAGATGATTGTGGAG | ACGTTGGATGCTTTATGACCTACAGT | 105                       | ggcAAATCTTTCTCACTGTGACATG     |
| AHR  | rs2158041 | ACGTTGGATGCTCCTTACTTACCTTCTC | ACGTTGGATGCTTTCTTAAACACCGTT | 106                       | GTGTCGGACATGACATCTT           |
| AHR  | rs6960165 | ACGTTGGATGGAAAGTGTAAGATGAGG | ACGTTGGATGGACATCTGCTCTTACCAC | 107                       | CAAACCCTAAAAGATGCTGTTG        |
| AHR  | rs7811989 | ACGTTGGATGCAAGTCACCTGAGAGA | ACGTTGGATGCTTTATGACCTACAGT | 82                        | GAGGAGGTCAGTGTGTCAGG          |
| AHR  | rs2292596 | ACGTTGGATGCGTTTCTGAGACTACAG | ACGTTGGATGCACTCTGAGAGGCTAG | 100                       | AGGTGCTGATGATGTCAGG          |
| ARNT | rs2228099 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCTTTATGACCTACAGT | 98                        | GCAGGGGCTGTATG                |
| BMAL1 | rs1102275 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCACTCTGAGAGGCTAG | 101                       | TCTCCTCAAACCTCAC             |
| BMAL1 | rs1122780 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCTTTATGACCTACAGT | 115                       | TCTCCTCAAACCTCAC             |
| BMAL1 | rs1481892 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCTTTATGACCTACAGT | 107                       | CAATCTTTCTATGCTGACT           |
| BMAL1 | rs1868049 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCTTTATGACCTACAGT | 100                       | TCCATAGCAGACAGACTACTT         |
| BMAL1 | rs2278749 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCTTTATGACCTACAGT | 100                       | GGAAGCGACTGACACTGACC          |
| BMAL1 | rs2279287 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCTTTATGACCTACAGT | 101                       | CCCCCGCGCCGGGCTGTGACTC       |
| BMAL1 | rs2290035 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCTTTATGACCTACAGT | 97                        | gttgTACTTTCTCAACTCTCCT        |
| BMAL1 | rs3816358 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCTTTATGACCTACAGT | 119                       | CCTCCATGCTGCACT                |
| BMAL1 | rs3816360 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCTTTATGACCTACAGT | 109                       | CCTCAAGACTTGGGCTTCAGG         |
| BMAL1 | rs4757142 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCTTTATGACCTACAGT | 95                        | CAGGAGGACTGACACAGACAGACAGA   |
| BMAL1 | rs4757144 | ACGTTGGATGCTTTATGACCTACAGT | ACGTTGGATGCTTTATGACCTACAGT | 103                       | aagaACGGGCTGATTTAAA           |
| Gene   | SNP ID   |美学一 | 5'端序列 | 3'端序列 | Length | 等位碱基 |
|--------|----------|-------|----------|----------|--------|----------|
| BMAL1  | rs6486120| ACGTTGGATGAGAGGCCCTTGCACTAGG | ACGTTGGATGAAATTTGGGCCTCATGTG | 114     | cGGCTCTGTGTTGTTTAT |
| BMAL1  | rs7126303| ACGTTGGATGAAAGGGACCTCACCACATCC | ACGTTGGATGGGAAGCCGCTTTAAAATC | 101     | GCCATCTCAAAGGCAAGT |
| BMAL1  | rs969485 | ACGTTGGATGGAAAGGGCCCATGTG | ACGTTGGATGAAATTTGGGCCTCATGTG | 100     | gcctcTAATGAACTGCAAGTCCT |
| CLOCK  | rs10002541| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 94      | tcGGCTCTGTGTTGTTTAT |
| CLOCK  | rs10462028| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 92      | TCGAGCATCCCAATTC |
| CLOCK  | rs1048004| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 90      | GTCTCCTTGGACTTTAGG |
| CLOCK  | rs11133373| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 107     | cTACTTGGCTTCCCTAG |
| CLOCK  | rs11133383| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 98      | ggGAGAAGAGACAAATAGT |
| CLOCK  | rs11133389| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 98      | catCTTCCAGTGGTGTG |
| CLOCK  | rs11133391| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 119     | cagtGAAACTGAGGAGATAT |
| CLOCK  | rs11240| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 99      | TCTGGTCTTCCGTTAAATA |
| CLOCK  | rs11726609| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 99      | gatAATAGTAGCTGCGACAGAAAGG |
| CLOCK  | rs11735267| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 109     | TAAAGGAGTGAAAAAGGAAAAAT |
| CLOCK  | rs11824092| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 100     | taCTGCGACACAGTGGG |
| CLOCK  | rs11931061| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 102     | cccctgATCTGCAAGCAGTACTGAGT |
| CLOCK  | rs11932595| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 104     | GTTTAGACCCCTGCC |
| CLOCK  | rs11943456| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 117     | aatgCTGAAACCCACACAGCCT |
| CLOCK  | rs12504300| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 114     | ATTTGGACTGATAAGGAAGT |
| CLOCK  | rs12648271| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 119     | cATGTGAGATTTAGTCTTCCTAAAGCC |
| CLOCK  | rs12649507| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 83      | GCCTAAATGCGAAGGAG |
| CLOCK  | rs13102385| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 114     | gttgACTGTATATTGGTAACCTGG |
| CLOCK  | rs13132420| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 99      | GCCTAGAGCTTTTCTCCTT |
| CLOCK  | rs17721497| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 97      | GTGGCACCCTGACA |
| CLOCK  | rs1801260| ACGTTGGATGAGGACCTCACCACATCC | ACGTTGGATGAAATTTGGGCCTCATGTG | 86      | ggaacTAAACACTGTCAGAACAGCCTG |

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| rs2070062 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 112 | TGGTTGGTCATAATAAGAGAG |
| rs2272073 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 118 | TTGGAGGCTTACTCTCA |
| rs2412646 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 110 | TGTTATATCAGGTCAGAAGT |
| rs2412648 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 91 | TCTCACACTCTAAGGAGGAA |
| rs3736544 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 102 | tattGGTGCAAGTTGCTGGAT |
| rs3749474 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 114 | ggCCCTACTTTACTTTTTCAATT |
| rs3762836 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 104 | ccTTCTCTCTGTTGCAGA |
| rs3792603 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 120 | GTTCTCTACCTTTAGGCT |
| rs3805147 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 87 | TCTTGACAATAAAAACCTCTATTTATA |
| rs3805148 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 92 | gGTGACTAAAGTGACTTTGAAAT |
| rs3805151 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 98 | ggTGGCAAGATAAAAAT |
| rs3817444 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 105 | cctgACAGGAAAGTAGCACTAT |
| rs4340844 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 111 | cccgAGGTATGCTATTTATATACAGC |
| rs4580704 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 98 | gGTGTCCCAAACCACCTATCTGCTCAT |
| rs4864546 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 94 | ggagGCTGTGTTCTTCTATTT |
| rs4864548 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 110 | GACAGTGAATAGGAGATG |
| rs534654 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 111 | cctcGCTGCTCTTGACAGGTA |
| rs6811250 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 99 | GGCTTTCTCAATAGATG |
| rs6832769 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 104 | GTGATTGGGAATGATTTTGTTATAGAA |
| rs6843722 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 116 | cagtGACGATTAGAAAAATGCAAGT |
| rs6850524 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 82 | CGGGAGTCACAAAGAT |
| rs6858749 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 99 | acGGAAGTTTAACCTGCTGAAAGG |
| rs726967 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 119 | AGTATACAGAAGAAATTCA |
| rs7660668 | ACGTTGGATGGCTTTTGTACTCTGGATCT | ACGTTGGATGGCTTTTGTACTCTGGATCT | 116 | TGGGCAACAAAGTCA |
| Gene      | SNP   | Sequence 1          | Sequence 2          | Length |
|-----------|-------|---------------------|---------------------|--------|
| CLOCK     | rs7698022 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 120    |
| CLOCK     | rs9312661 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 120    |
| CYP1A2*1B | rs2470890 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 114    |
| CYP1A2*1C | rs2069514 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 112    |
| CYP1A2*1D | rs3569413 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 107    |
| CYP1A2*1E | rs2069526 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 111    |
| CYP3A4     | rs4646437 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 90     |
| CYP3A4*18A | rs28371759 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 109    |
| CYP3A4*1B  | rs2740574 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 101    |
| CYP3A4*23  | rs2687116 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 110    |
| CYP3A4*23  | rs3735451 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 101    |
| CYP3A4*4   | rs55951658 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 116    |
| CYP3A4*2A  | rs61469810 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 101    |
| CYP3A4*3   | rs680055  | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 112    |
| CYP3A5*4   | rs56411402 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 113    |
| CYP3A5*5   | rs59965422 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 105    |
| CYP3A7     | rs1021   | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 119    |
| CYP3A7     | rs12360  | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 100    |
| CYP3A7*1D  | rs55798860 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 107    |
| CYP3A7*2   | rs2257401 | ACGTTGGATGTTGAACTTCTTGTTGAAACAGG | ACGTTGGATGAGGCTATAAACAGTAAAGT | 100    |

**Abbreviations:** AHR, aryl hydrocarbon receptor; AHRR, aryl-hydrocarbon receptor repressor; ARNT, aryl hydrocarbon receptor nuclear translocator; BMAL1, aryl hydrocarbon receptor nuclear translocator-like protein 1 or Brain and Muscle ARNT-Like 1; CLOCK, circadian Locomotor Output Cycles Kaput.
### Table 2: Single nucleotide polymorphisms (SNPs) association with preterm infants in bronchopulmonary dysplasia (BPD) group and BPD-free group

| Gene   | SNPs         | Model | Genotype | Frequency no. (%) | BPD group no. (%) | BPD -free group no. (%) | Odds ratio | 95% CI     | p     |
|--------|--------------|-------|----------|-------------------|-------------------|-------------------------|------------|-----------|-------|
| ADORA1 | rs16851030   | C>T   | CC       | 45 (40.91)        | 17 (58.6)         | 28 (34.6)               | 1          | 1.00      | 0.25  |
|        | rs2236625    | G>A   | CC       | 92 (82.88)        | 28 (96.5)         | 64 (78)                 | 1          | 1.00      | 0.01  |
|        | rs34923252   | T>A   | TT       | 94 (83.93)        | 28 (96.5)         | 66 (79.5)               | 1          | 1.00      | 0.015 |
|        | rs5760425    | T>G   | TT       | 31 (27.93)        | 4 (13.8)          | 27 (32.9)               | 1          | 1.00      | 0.038 |
|        | rs5996696    | A>C   | AA       | 94 (83.93)        | 28 (96.5)         | 66 (79.5)               | 1          | 1.00      | 0.15  |
| ADORA2A| rs2298383    | C>T   | CC       | 31 (27.93)        | 4 (13.8)          | 27 (32.9)               | 1          | 1.00      | 0.038 |
|        | rs4822492    | C>G   | CC       | 79 (71.82)        | 4 (13.8)          | 27 (33.3)               | 1          | 1.00      | 0.035 |
|        | rs5751876    | T>C   | TT       | 31 (27.93)        | 4 (13.8)          | 27 (32.9)               | 1          | 1.00      | 0.038 |
|        | rs5760423    | T>G   | TT       | 31 (27.93)        | 4 (13.8)          | 27 (32.9)               | 1          | 1.00      | 0.038 |
| ADORA3 | rs10776727   | C>A   | CC       | 40 (36.36)        | 6 (20.7)          | 34 (42)                 | 1          | 1.00      | 0.035 |
| BMAL1  | rs4757144    | G>A   | GG       | 38 (34.55)        | 5 (18.5)          | 33 (39.8)               | 1          | 1.00      | 0.036 |
| PDE1A  | rs1549870    | G>A   | GG       | 54 (49.54)        | 19 (65.5)         | 35 (43.8)               | 1          | 1.00      | 0.043 |
| PDE4A  | rs6511698    | C>T   | CC       | 27 (24.32)        | 3 (10.3)          | 24 (29.3)               | 1          | 1.00      | 0.03  |
|        |              |       | TC/TT    | 84 (75.68)        | 26 (89.7)         | 58 (70.7)               | 0.28       | 0.08-01   | 0.03  |
| ADORA2A| rs4822489    | G>A   | GG       | 34 (30.36)        | 7 (24.1)          | 27 (32.5)               | 1          | 1.00      | 0.028 |
|        | rs7811989    | G>A   | AG       | 76 (65.45)        | 22 (81.5)         | 50 (60.2)               | 0.34       | 0.12-1.00 | 0.0054|
| AHR    | rs966221     | A>G   | AA       | 62 (53.86)        | 17 (58.6)         | 45 (54.9)               | 1          | 1.00      | 0.019 |
|        |              |       | AG       | 44 (39.64)        | 8 (27.6)          | 36 (43.9)               | 1          | 1.00      | 0.019 |
| PDE4D  | rs2290035    | T>A   | TT       | 46 (48.94)        | 8 (33.3)          | 38 (54.3)               | 1          | 1.00      | 0.0066|
| BMAL1  | rs762551     | A>C   | AA       | 49 (44.14)        | 17 (58.6)         | 32 (39)                 | 1          | 1.00      | 0.033 |
| CYP1A2 | rs2472299    | G>A   | AA       | 49 (44.14)        | 17 (58.6)         | 32 (39)                 | 1          | 1.00      | 0.033 |

Notes:
- Dominant model: CC/TT vs. GC/GT
- Codominant model: AA/AG/TT vs. GG/GT
Data from BPD group was defined as case group and data from BPD-free group was defined as control group for the association analysis.

Abbreviations: BPD, bronchopulmonary dysplasia; ADORA1, Adenosine A1 receptor gene; ADORA2A, Adenosine A2A receptor gene; ADORA3, Adenosine A3 receptor gene; BMAL1, aryl hydrocarbon receptor nuclear translocator-like protein 1 or Brain and Muscle ARNT-Like 1; PDE1A, Phosphodiesterase 1A gene; PDE4A, Phosphodiesterase 4A gene; PDE4D, Phosphodiesterase 4D gene; AHR, Aryl hydrocarbon receptor gene; CI, Confidence interval.
Table 3 Single nucleotide polymorphisms (SNPs) association with preterm infants in severe neurological injury (SNI) group and SNI-free group†

| Gene       | SNPs         | Model         | Genotype | Frequency no. (%) | SNI group no. (%) | SNI-free group no. (%) | Odds ratio | 95% CI       | p      |
|------------|--------------|---------------|----------|------------------|-------------------|------------------------|------------|--------------|--------|
| ADA        | rs2472304 G>A| Dominant      | GG       | 79 (71.17)       | 11 (52.4)         | 68 (75.6)              | 1          | 0.041        |        |
|            |              |               | GA/AA    | 32 (28.83)       | 10 (47.6)         | 22 (24.4)              | 0.36       | 0.13-0.95    |        |
| ADORA2A    | rs5760410 A>G| AA            | 32 (29.36) | 8 (36.4)         | 24 (27.6)         | 1                      |            | 0.043        |        |
|            |              | GA            | 53 (48.62) | 13 (59.1)        | 40 (46)           | 1.03                   | 0.37-2.83  | 0.011        |        |
|            |              | GG            | 24 (22.02) | 1 (4.5)          | 23 (26.4)         | 7.67                   | 0.89-66.20 |            |        |
| AHRR       | rs2292596 C>G| CC            | 55 (49.55) | 14 (66.7)        | 41 (45.6)         | 1                      |            | 0.11         |        |
|            |              | CG            | 38 (34.23) | 7 (33.3)         | 31 (34.4)         | 1.51                   | 0.55-4.19  |            |        |
|            |              | GG            | 18 (16.22) | 0 (0)            | 18 (20)           | NA                     | 0.00-NA    |            |        |
| CLOCK      | rs2070062 A>C| AA            | 91 (82.73) | 18 (85.7)        | 73 (82)           | 1                      |            | 0.01         |        |
|            |              | CA            | 17 (15.45) | 1 (4.8)          | 16 (18)           | 3.95                   | 0.49-31.74 |            |        |
|            |              | CC            | 2 (1.82)   | 2 (9.5)          | 0 (0)             | 0                      | 0.00-NA    |            |        |
| BMAL1      | rs4757142 G>A| GG            | 49 (44.14) | 10 (47.6)        | 39 (43.3)         | 1                      |            | 0.032        |        |
|            |              | AG            | 48 (43.24) | 5 (23.8)         | 43 (47.8)         | 2.21                   | 0.69-7.02  |            |        |
|            |              | AA            | 14 (12.61) | 6 (28.6)         | 8 (8.9)           | 0.34                   | 0.10-1.21  |            |        |

† Data from SNI group was defined as case group and data from SNI-free group was defined as control group for the association analysis.

**Abbreviations:** SNI, Severe neurological injury; ADA, Adenosine deaminase gene; ADORA2A, Adenosine A2A receptor gene; AHRR, aryl-hydrocarbon receptor repressor; CLOCK, circadian Locomotor Output Cycles Kaput; BMAL1, aryl hydrocarbon receptor nuclear translocator-like protein 1 or Brain and Muscle ARNT-Like 1; CI, Confidence interval.