

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-PCR	2nd-PCR	Amplification length (bp)	UEP_SEQ
<i>AHR</i>	rs10249788	ACGTTGGATGTGCCCCGCCCATCTGGATT	ACGTTGGATGCTTACGTCCTACGTCATCAC	101	GGCCCTCAAGGAAGA
<i>AHR</i>	rs10250822	ACGTTGGATGCTCCTTTATCTACTTTCTG	ACGTTGGATGGACATAAATCCTGTCTACTG	98	GTCTACTGATACATTATAAAGTCT
<i>AHR</i>	rs1476080	ACGTTGGATGACCACTATTCGGTATTCCTC	ACGTTGGATGCTCCCTAAATGCCACATCTC	104	ggacTGCCACATCTCTTCATATC
<i>AHR</i>	rs2066853	ACGTTGGATGCCTAGGCATTGATTTGAAG	ACGTTGGATGTCTGAAGTCAACCTCACCAG	105	gggcAAAATTTTTCATTCTGCATGTGT
<i>AHR</i>	rs2158041	ACGTTGGATGCTTGATGCCAACCATACAC	ACGTTGGATGTGAAGGGTTTTGTTACAGGG	106	GTGTTTCAGATGCAACTTT
<i>AHR</i>	rs6960165	ACGTTGGATGGAATGAACAGTGAATAGATGG	ACGTTGGATGGTTACAATCTGTTCTCAAACC	107	CAAACCATAAAAGATGTTCTTG
<i>AHR</i>	rs7811989	ACGTTGGATGCAAGTCCACTCTGAGGAATC	ACGTTGGATGTCTGAACACCTGCATAGGAG	82	gGGAGTTGACTGTAGGGA
<i>AHRR</i>	rs2292596	ACGTTGGATGGGTTTTGCTGACTCACTTGG	ACGTTGGATGACCTCCCCAGGTGGTGTTT	100	AGGTGGTGTGGGCAG
<i>ARNT</i>	rs2228099	ACGTTGGATGATTGAGCTGTGGCTGGTTC	ACGTTGGATGTTGTCTCATGTGAGACAGGC	98	GCAGGGTGGTGTATGT
<i>BMAL1</i>	rs11022775	ACGTTGGATGCTAAGAAGCAGAGTCTCAG	ACGTTGGATGGGACTTCATACTTTGCCCTC	101	TCTCCTCAAACCTCCATC
<i>BMAL1</i>	rs1122780	ACGTTGGATGCTAGCAACATACCTGTTGTG	ACGTTGGATGCTTTATCCTTGAGTCATTC	115	CTTGAGTCATTCATATTTTAGTG
<i>BMAL1</i>	rs1481892	ACGTTGGATGCCCTTCACACCAACAATCTC	ACGTTGGATGGCAGTTTTGTTAATACAGCC	107	CAAATCTTCTATGGTGCTT
<i>BMAL1</i>	rs1868049	ACGTTGGATGGCACTATATTGGGTTGTGGG	ACGTTGGATGGTTTGCCACACACTTTCC	100	ttcatAGCCACATGCATTTGCT
<i>BMAL1</i>	rs2278749	ACGTTGGATGAACCCACCTATGTTAAGAG	ACGTTGGATGATCATTACAGCACCTCTCC	100	ggaagGCAGTGCACCTAGCCCC
<i>BMAL1</i>	rs2279287	ACGTTGGATGAGTAGCCAGGTTTTGACCAC	ACGTTGGATGCCGTAGACAGCTTTTGCAG	101	ccccGCCGCGGGGCTGGTGTCTAC
<i>BMAL1</i>	rs2290035	ACGTTGGATGGGAGTTACAAAAAGAAAGGC	ACGTTGGATGTTTTCTCCCCTGGGCTTTC	97	gttgTTTTCTAACTCTCCCT
<i>BMAL1</i>	rs3816358	ACGTTGGATGTTCTGGCTGGCCAGAGTG	ACGTTGGATGTTTTAGCTCTCTCTCTGC	119	CCTCTGCTCCCACT
<i>BMAL1</i>	rs3816360	ACGTTGGATGCAACCAAGTGAATGAGGGCAG	ACGTTGGATGATTGACAGTCATGGGCACAG	109	cctcAAAGGTCCTTTAGAAAGTTGTGGC
<i>BMAL1</i>	rs4757142	ACGTTGGATGTCAGTCCACTCTCAACACAG	ACGTTGGATGTTTGAAGGAGGAACGACAGG	95	tgagtAGGAACGACAGGATCTGAGGCAC
<i>BMAL1</i>	rs4757144	ACGTTGGATGGGTTTCTAGACTGTAGGC	ACGTTGGATGTAGTGTCTAGGCAGTTGGG	103	aagaACGGGGTGAATTTAACAG

<i>BMAL1</i>	rs6486120	ACGTTGGATGAGAGGCCTCTTGCATCATGG	ACGTTGGATGTGGAAAATTGGGCCATGTG	114	cGGCTCTGTGTGTGGTTTAT
<i>BMAL1</i>	rs7126303	ACGTTGGATGAAAAGGGTCACCCACATCC	ACGTTGGATGGGAAAGCCCGTTTAAATC	101	GCCATCTCAAGGCAGTG
<i>BMAL1</i>	rs969485	ACGTTGGATGATGTGAGTGAAGAAGGGAG	ACGTTGGATGGGAACTCTTGAATTGCTCCC	100	gctccATTAAATGAACTGACAGTTCC
<i>CLOCK</i>	rs10002541	ACGTTGGATGTTTCGGAGCTTCCAATTGCC	ACGTTGGATGAGAACTGGGTCTTCTGGTG	94	tgccgGGGTCTTCTGGTGTCAATG
<i>CLOCK</i>	rs10462028	ACGTTGGATGATGACAAAGGAGAGCACAGC	ACGTTGGATGATACTACGGTCTAGCCTTCG	92	TCGAGCATCCCAAATTC
<i>CLOCK</i>	rs1048004	ACGTTGGATGGATAGTGTTAGGTTATCATC	ACGTTGGATGGACTGCTATCAGTCTCTTGG	90	gGTCTCTTGGACTGGAG
<i>CLOCK</i>	rs11133373	ACGTTGGATGCCCATTTCTGCAAATAAGGC	ACGTTGGATGTTTCAGGTTTTACTCTTGCC	107	cTACTCTTGCCCTCCGTAG
<i>CLOCK</i>	rs11133385	ACGTTGGATGTCAAGCTCCCTTCGTCTATG	ACGTTGGATGGTGATGGGAAGAGAAGAGAC	98	ggGAGAAGAGACCAAATTGTAA
<i>CLOCK</i>	rs11133389	ACGTTGGATGGGATCAGTAATCAGAATGGC	ACGTTGGATGCTGAATGCTGAAGACTCCAC	98	tatCTTCCAGTGTGGTGT
<i>CLOCK</i>	rs11133391	ACGTTGGATGGGAAATTACAAATATACAC	ACGTTGGATGGATTGATTAGCCATGAGTTG	119	cagtGAAACTGGGTGAAGGATAT
<i>CLOCK</i>	rs11240	ACGTTGGATGAGATGAACAGATGAGACACG	ACGTTGGATGTTTTAGTGTCTGGTCATTCG	99	TCTGGTCATTCGTTTAAATA
<i>CLOCK</i>	rs11726609	ACGTTGGATGTGGTGGTCTTCATCTGTTC	ACGTTGGATGCCCAGCAGACAGAATAGTAG	99	gataAATAGTAGCTGGCAGACAACAGAA
<i>CLOCK</i>	rs11735267	ACGTTGGATGATTGGTGGCTAACTCAACCC	ACGTTGGATGGGCTAAAGGAGTGAATAGGG	109	TAAAGGAGTGAATAGGGAATTTAT
<i>CLOCK</i>	rs11824092	ACGTTGGATGCAGTCATTTGTCCATCCACC	ACGTTGGATGAGCACTCTAGGGCCTAAAC	100	taCTGGCACACAGTGGG
<i>CLOCK</i>	rs11931061	ACGTTGGATGGTTACTCTAACTCCCAGCTC	ACGTTGGATGAATCCTTGATCTGCAGCAC	102	ccctgATCTGCAGCACTAGTGTAGC
<i>CLOCK</i>	rs11932595	ACGTTGGATGATGAGTTGAAGGACAGGGAG	ACGTTGGATGCATCCATCTTGAGTGCATTG	104	GTTTAGACCCCTGCC
<i>CLOCK</i>	rs11943456	ACGTTGGATGCCCTCCTTTCTCTTCTTC	ACGTTGGATGGCAAGTTACTGAACCAAAACC	117	aatgCTGAACCAAAACCCAGCCT
<i>CLOCK</i>	rs12504300	ACGTTGGATGACCTTTTCCCAAGAGTATG	ACGTTGGATGGCATCTTAGCATTTGTGACTG	114	ATTGTGACTGATAAGAAGTAA
<i>CLOCK</i>	rs12648271	ACGTTGGATGCCATCTGTAAACAGTCCAGT	ACGTTGGATGGTCTTTGTGACTTCGTAAG	119	cTATTGTAGTTATGTTTTATAAAAGCC
<i>CLOCK</i>	rs12649507	ACGTTGGATGCATATCCCAATACCAACACC	ACGTTGGATGGGGACATAACAGCCTAAATG	83	GCCTAAATGCAGTAAAGAG
<i>CLOCK</i>	rs13102385	ACGTTGGATGCATGACACAGCATGTACTTC	ACGTTGGATGGAGCTGAAAAATTATTGCC	114	gttgACTGTATATTGGTAACCTGG
<i>CLOCK</i>	rs13132420	ACGTTGGATGTCATACTACTGTGTCTGCCC	ACGTTGGATGCCCGCCTAGAGCTTTTTTT	99	GCCTAGAGCTTTTTTTTCTTA
<i>CLOCK</i>	rs17721497	ACGTTGGATGACACTGCCAAGAAAGTGCTC	ACGTTGGATGTAAAAGCTTCCCGTTGGCAC	97	GTTGGCACCTGACA
<i>CLOCK</i>	rs1801260	ACGTTGGATGTAAATACCAGCCAGCAGGAG	ACGTTGGATGCAGGCACCTAAAACACTGTC	86	ggaaCTAAACACTGTCAGAACTGGCT

CLOCK	rs2070062	ACGTTGGATGCCTTTTGTACTCCTTGGATCT	ACGTTGGATGATTCTGAGACTTATGGTTGG	112	TGGTTGGTCATATAGAAGAG
CLOCK	rs2272073	ACGTTGGATGTTACGGTTGAGTTCCAGAG	ACGTTGGATGTAGAACATTTATTGCGAGCC	118	TTGCGAGCCTCCTCTA
CLOCK	rs2412646	ACGTTGGATGGGAGTAAGTTGTTACACAGC	ACGTTGGATGAGTCAGAATTGGAACCTCTGG	110	TGTTATATCAGGTCAGAAGT
CLOCK	rs2412648	ACGTTGGATGCTAGCTGGGTAACCTTTGGAC	ACGTTGGATGACCGCCTCTCACTCTCTAAG	91	TCTCACTCTCTAAGGAGGAAA
CLOCK	rs3736544	ACGTTGGATGGGTTCCGTTCAACTTTCTTC	ACGTTGGATGTAGGAACAACCTTGGCCTTGC	102	tatcGGTGCAAGTTGCTGGAT
CLOCK	rs3749474	ACGTTGGATGAATCAAACTCCCAGCCACC	ACGTTGGATGGTTATTAGAAATATCCCTC	114	ggCCCTCATTTTCATTATTTTCAATTAT
CLOCK	rs3762836	ACGTTGGATGACGGACACGCATGATAGAAG	ACGTTGGATGCCATGGACCATCTGAAGTTG	104	ccTTCTTCTGTTGCCGA
CLOCK	rs3792603	ACGTTGGATGCTGGCCTCAGAGTATTTGTT	ACGTTGGATGCACACACGTTCTTTCACTTT	120	GTTCTTTCACTTTATGTCCT
CLOCK	rs3805147	ACGTTGGATGGCATTAAAGTATTTGGTTG	ACGTTGGATGCACCTAGTACAGATCTTGAC	87	TCTTGACAATAAAATACTCTATTTTATA
CLOCK	rs3805148	ACGTTGGATGGTCCATATTAAGAAAGTCC	ACGTTGGATGGCACTTAGTACTTCTGTGAC	92	gGTGACTAAGTGACTTTGTAAATA
CLOCK	rs3805151	ACGTTGGATGGACAGAACTTTGGATATTTT	ACGTTGGATGAAAGTATTTTGCAGGACAG	98	ggTGCAGGACAGAAATAAAAAAT
CLOCK	rs3817444	ACGTTGGATGGAATTTGCAGTGACCGGTG	ACGTTGGATGAAAGCTGCCAAGGAAAGTAG	105	cctgaCAAGGAAAGTAGCAGATCATT
CLOCK	rs4340844	ACGTTGGATGCATTAGGCCACTCTAGTCTG	ACGTTGGATGTCCATTCCATCCATGGCTTC	111	cccgAGGTATCTATTATATACAGCCTA
CLOCK	rs4580704	ACGTTGGATGGCACTAAATTGGCAGGCTTC	ACGTTGGATGTCCATCACAAGTCCCAAAC	98	gggtTCCCAAACCTAATCTGTCAT
CLOCK	rs4864546	ACGTTGGATGAACCCAAAAGTAAGCTGAGG	ACGTTGGATGGTTTAATTGACTGCCTGTGG	94	ggagGCCTGTGGTTTTCTTATTTT
CLOCK	rs4864548	ACGTTGGATGAGGGTCTGGTTTATTTCTG	ACGTTGGATGTGGAGATTTTCCCTTGCCC	110	GACAGTGTAATGGAAGATG
CLOCK	rs534654	ACGTTGGATGCTCAGTGCCAGGAATCAAGG	ACGTTGGATGTTACTACATACCCCTCTCCC	111	cctcGTCTGCTTTGCTCAGGTA
CLOCK	rs6811520	ACGTTGGATGACTTACCATTGCCTCATAC	ACGTTGGATGATAGGGAACAGGCCTTTCCA	99	GGCCTTTCCAATATAGATG
CLOCK	rs6832769	ACGTTGGATGCTACAGCACTTCTGAAGACC	ACGTTGGATGCAAGATGCCAGTGATTTGGA	104	GTGATTTGGAATAGTTTGTATAGAA
CLOCK	rs6843722	ACGTTGGATGAGCCAACCATGGATCAAAAC	ACGTTGGATGAGTGTTTAGGGAACGATTAG	116	cagtGAACGATTAGAAAAATGCACGTA
CLOCK	rs6850524	ACGTTGGATGCCACGCTATAAATTTCCCTC	ACGTTGGATGCAACTTAACAAAATATGCGGG	82	CGGGATGCAACAAATG
CLOCK	rs6858749	ACGTTGGATGAGTCAACAAATCCTGATG	ACGTTGGATGGCTACGTATTGCCTGTGAAG	99	acGGAAGTTTAATAACTGCTGAAAGG
CLOCK	rs726967	ACGTTGGATGCCTTCTGCAGTGACTAATG	ACGTTGGATGGCAGAGGTGAGAAAAATATA	119	AGTAATCACAGAAGAATTCATCA
CLOCK	rs7660668	ACGTTGGATGCCTAAGTGCAGACAATTTCC	ACGTTGGATGAGGAGTTCAAGACAAGCCTG	116	TGGGCAACAAAGTCA

<i>CLOCK</i>	rs7698022	ACGTTGGATGGTGTAACTTCTGTGAAACAGG	ACGTTGGATGGAGGCTATAAGAGTAAGTT	120	ccacAAAATGGAAAAAACAGGAATCTC
<i>CLOCK</i>	rs9312661	ACGTTGGATGAGGAGTACAAAAGCCCTACA	ACGTTGGATGGGACCTCTTGATATCTACCC	120	cctcCCCAATAAATGTTAATGCCTA
<i>CYP1A2*1B</i>	rs2470890	ACGTTGGATGGCCTCAGAAATGGTGGTGTCT	ACGTTGGATGTCTACGGGCTGACCATGAAG	114	TGCGCTTCTCCATCAA
<i>CYP1A2*1C</i>	rs2069514	ACGTTGGATGAGTGCAGTGGTGCATCTTG	ACGTTGGATGTGTAATTCCAGCTACTCGGG	112	cgggtCATGACAATTGCTTGAATC
<i>CYP1A2*1D</i>	rs35694136	ACGTTGGATGGATTGTTGAGCTCAGGAGG	ACGTTGGATGACAGAGTCTTGCTCTGTAC	107	ggtaACCCAGGTTGGGGTTC
<i>CYP1A2*1E</i>	rs2069526	ACGTTGGATGTAGAACCTGGAAGCTAGTGG	ACGTTGGATGTCAAGAGCTGGGTAGCAAAG	111	cccAGCCCGGAAGCTCAGG
<i>CYP3A4</i>	rs4646437	ACGTTGGATGAGGGCAGGTCTATGCATAAG	ACGTTGGATGCTTCAAAAGATGCACAAGGG	90	TGATCTCACTGCTGTAG
<i>CYP3A4*18A</i>	rs28371759	ACGTTGGATGCACTGCTCGTGGTTTCATAG	ACGTTGGATGCTTCTCCTCTCTTCAGCTC	109	gttgCAGCTCTGTCCGATC
<i>CYP3A4*1B,</i>	rs2740574	ACGTTGGATGATGAGGACAGCCATAGAGAC	ACGTTGGATGATCAGAACTCAAGTGGAGC	101	TCTATTAAATCGCCTCTCTC
<i>CYP3A4*23</i>	rs2687116	ACGTTGGATGAGTGGATGAATTACATGGTG	ACGTTGGATGGTATGTGGACTACTATTTC	110	TGGACTACTATTTCTTTTATTATCTT
<i>CYP3A4*23</i>	rs3735451	ACGTTGGATGTACTGCATTTTTTTTGCCC	ACGTTGGATGGAGACACTCCTTCAGTGTG	101	gggCAACAGAGTGATATTCTGATCTC
<i>CYP3A4*4</i>	rs55951658	ACGTTGGATGGTTGGAGACAGCAATGATCG	ACGTTGGATGACTCTAGCCTTTTGGTCCAG	116	aAGTGGGATTATGAAAAGTGCC
<i>CYP3A43*2A</i>	rs61469810	ACGTTGGATGCCAGGAATCCAGCTTCTT	ACGTTGGATGTTCTGTAACCTGGCTTCTC	101	CTGGCTTTCTCTTTTATTTATAGTT
<i>CYP3A43*3</i>	rs680055	ACGTTGGATGAACTGCAGGAGGAGATTGAC	ACGTTGGATGATTCTTGCTGAGGCTTCACC	112	tctaATCCCCTTACCTTATTGG
<i>CYP3A5*4</i>	rs56411402	ACGTTGGATGGCATGGATGTGATTACTGGC	ACGTTGGATGGGAACCTCTTAGTGCTCTCC	113	TCCACAAAGGGGTCT
<i>CYP3A5*5</i>	rs55965422	ACGTTGGATGACCTGTCCCAGATTCATTC	ACGTTGGATGAACCTTCACCAGCGGAAAAC	105	gactgCACCAGCGGAAAACCAAGGAGG
<i>CYP3A7</i>	rs1021	ACGTTGGATGAAGCGGTAAGTTCAGAC	ACGTTGGATGGGTGAAATGTAGAATAAGGC	119	ccccATAAGGCCTTCAACTTTTTTT
<i>CYP3A7</i>	rs12360	ACGTTGGATGTTGAGGTCTCTGGTGTCTG	ACGTTGGATGCGTAAGTGGAGCCTGATTC	100	ggggaACTTCTGGTTTGCTCTT
<i>CYP3A7*1D</i>	rs55798860	ACGTTGGATGACAGCCTCACTGAATCACTG	ACGTTGGATGGTCTTTTTTTCAGCAGCGTG	107	tgcgGTGTGTGTGGAGCTTTCCTGC
<i>CYP3A7*2</i>	rs2257401	ACGTTGGATGCTTTCAGGGAGGAACCTCTC	ACGTTGGATGGTGGTGGTGATGATTCCAAG	100	cTCATGACCCAAAGTACTGGA

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	<i>p</i>	
ADORA1	rs16851030 C>T	Dominant	CC	45 (40.91)	17 (58.6)	28 (34.6)	1		0.025	
			TC/TT	65 (59.09)	12 (41.4)	53 (65.4)	2.68	1.12-6.40		
	rs2236625 G>A		CC	92 (82.88)	28 (96.5)	64 (78)	1		0.01	
			TC/TT	19 (17.12)	1 (3.5)	18 (21.9)	7.87	1.00-61.91		
	rs34923252 T>A		TT	94 (83.93)	28 (96.5)	66 (79.5)	1		0.015	
			TA/AA	18 (16.07)	1 (3.5)	17 (20.5)	7.21	0.91-56.85		
	rs5760425 T>G		TT	31 (27.93)	4 (13.8)	27 (32.9)	1		0.038	
			GT/GG	80 (72.07)	25 (86.2)	55 (67.1)	0.33	0.10-1.03		
	ADORA2A		rs5996696 A>C	AA	94 (83.93)	28 (96.5)	66 (79.5)	1		0.015
				CA/CC	18 (16.07)	1 (3.5)	17 (20.5)	7.21	0.91-56.85	
rs2298383 C>T		CC	31 (27.93)	4 (13.8)	27 (32.9)	1		0.038		
		CT/TT	80 (72.07)	25 (86.2)	55 (67.1)	0.33	0.10-1.03			
rs4822492 C>G		CC	79 (71.82)	4 (13.8)	27 (33.3)	1		0.035		
		CG/GG	31 (28.18)	25 (86.2)	54 (66.7)	0.32	0.10-1.01			
rs5751876 T>C		TT	31 (27.93)	4 (13.8)	27 (32.9)	1		0.038		
		CT/CC	80 (72.07)	25 (86.2)	55 (67.1)	0.33	0.10-1.03			
		rs5760423 T>G	TT	31 (27.93)	4 (13.8)	27 (32.9)	1		0.038	
			GT/GG	80 (72.07)	25 (86.2)	55 (67.1)	0.33	0.10-1.03		
ADORA3	rs10776727 C>A	CC	40 (36.36)	6 (20.7)	34 (42)	1		0.035		
		CA/AA	70 (63.64)	23 (79.3)	47 (58)	0.36	0.13-0.98			
BMAL1	rs4757144 G>A	GG	38 (34.55)	5 (18.5)	33 (39.8)	1		0.036		
		AG/AA	72 (65.45)	22 (81.5)	50 (60.2)	0.34	0.12-1.00			
PDE1A	rs1549870 G>A	GG	54 (49.54)	19 (65.5)	35 (43.8)	1		0.043		
		AG/AA	55 (50.46)	10 (34.5)	45 (56.2)	2.44	1.01-5.91			
PDE4A	rs6511698 C>T	CC	27 (24.32)	3 (10.3)	24 (29.3)	1		0.03		
		TC/TT	84 (75.68)	26 (89.7)	58 (70.7)	0.28	0.08-1.01			
ADORA2A	rs4822489 G>A	GG	34 (30.36)	7 (24.1)	27 (32.5)	1		0.028		
		GT	47 (41.96)	18 (62.1)	29 (34.9)	0.42	0.15-1.16			
		TT	31 (27.68)	4 (13.8)	27 (32.5)	1.75	0.46-6.68			
AHR	rs7811989 G>A	GG	67 (59.82)	13 (44.8)	54 (65.1)	1		0.0054		
		AG	38 (33.93)	16 (55.2)	22 (26.5)	0.33	0.14-0.80			
		AA	7 (6.25)	0 (0)	7 (8.4)	NA	0.00-NA			
PDE4D	rs966221 A>G	AA	62 (55.86)	17 (58.6)	45 (54.9)	1		0.019		
		AG	44 (39.64)	8 (27.6)	36 (43.9)	1.7	0.66-4.39			
		GG	5 (4.5)	4 (13.8)	1 (1.2)	0.09	0.01-0.91			
BMAL1	rs2290035 T>A	TT	46 (48.94)	8 (33.3)	38 (54.3)	1		0.0006		
		AT	36 (38.3)	16 (66.7)	20 (28.6)	0.26	0.10-0.72			
		AA	12 (12.77)	0 (0)	12 (17.1)	NA	0.00-NA			
CYP1A2	rs762551 A>C	AA	49 (44.14)	17 (58.6)	32 (39)	1		0.033		
		AC	45 (40.54)	6 (20.7)	39 (47.6)	3.45	1.22-9.78			
		CC	17 (15.32)	6 (20.7)	11 (13.4)	0.97	0.31-3.09			
	rs2472299 G>A	GG	49 (44.14)	17 (58.6)	32 (39)	1		0.033		
		AG	45 (40.54)	6 (20.7)	39 (47.6)	3.45	1.22-9.78			
		AA	17 (15.32)	6 (20.7)	11 (13.4)	0.97	0.31-3.09			

[†] 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	<i>p</i>
ADA	rs2472304 G>A	Dominant	GG	79 (71.17)	11 (52.4)	68 (75.6)	1		
			GA/AA	32 (28.83)	10 (47.6)	22 (24.4)	0.36	0.13-0.95	0.041
ADORA2A	rs5760410 A>G	Dominant	AA	32 (29.36)	8 (36.4)	24 (27.6)	1		
			GA	53 (48.62)	13 (59.1)	40 (46)	1.03	0.37-2.83	0.043
			GG	24 (22.02)	1 (4.5)	23 (26.4)	7.67	0.89-66.20	
AHRR	rs2292596 C>G	Codominant	CC	55 (49.55)	14 (66.7)	41 (45.6)	1		
			CG	38 (34.23)	7 (33.3)	31 (34.4)	1.51	0.55-4.19	0.011
			GG	18 (16.22)	0 (0)	18 (20)	NA	0.00-NA	
CLOCK	rs2070062 A>C	Codominant	AA	91 (82.73)	18 (85.7)	73 (82)	1		
			CA	17 (15.45)	1 (4.8)	16 (18)	3.95	0.49-31.74	0.01
			CC	2 (1.82)	2 (9.5)	0 (0)	0	0.00-NA	
BMAL1	rs4757142 G>A	Codominant	GG	49 (44.14)	10 (47.6)	39 (43.3)	1		
			AG	48 (43.24)	5 (23.8)	43 (47.8)	2.21	0.69-7.02	0.032
			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.