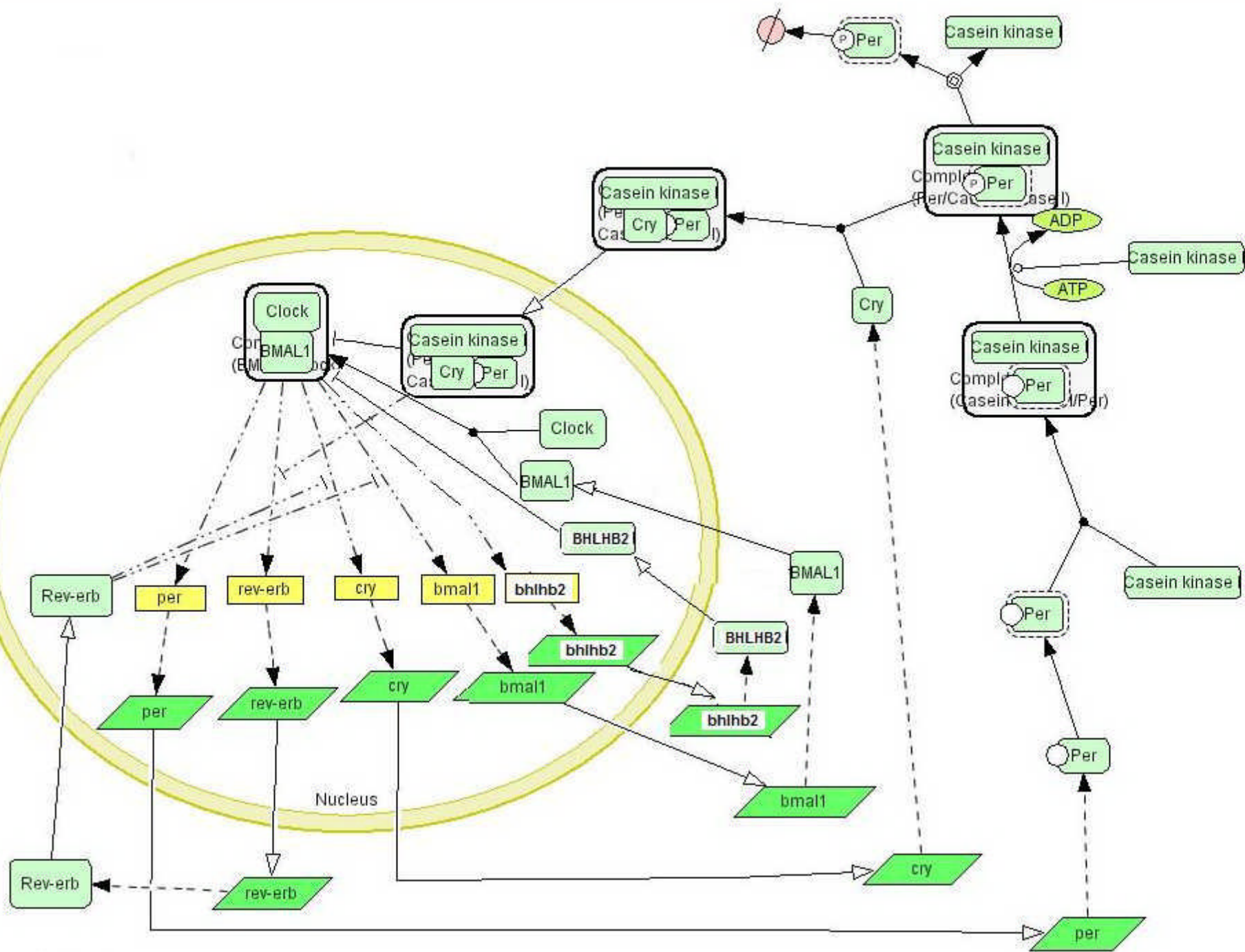


Type of file: figure

Label: 10

Filename: Suppl Figure 1.JPG

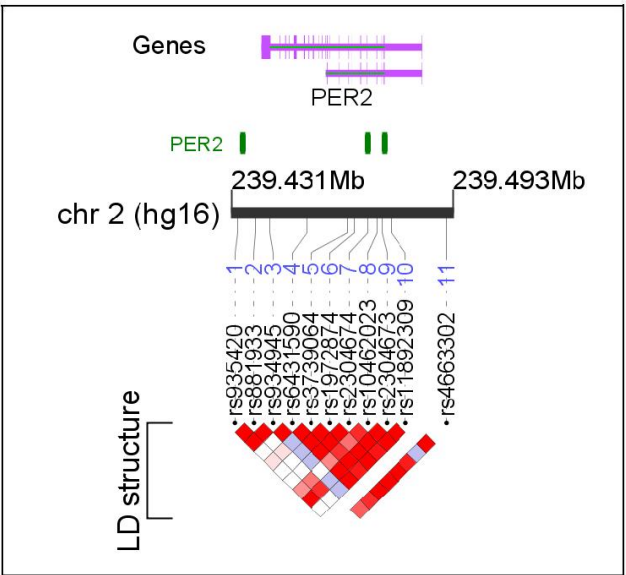
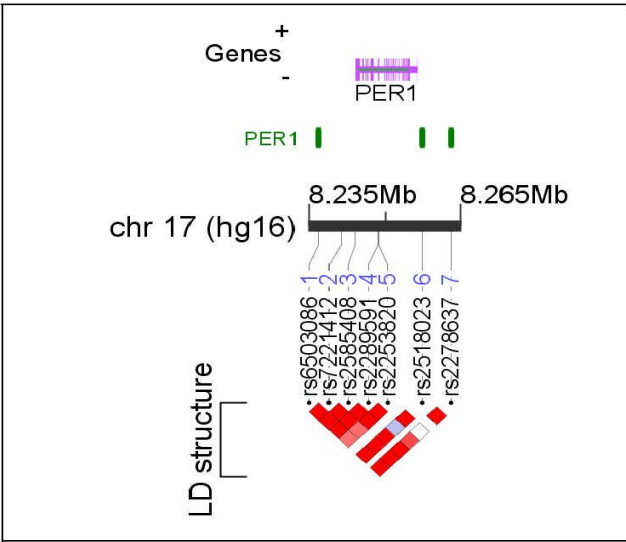
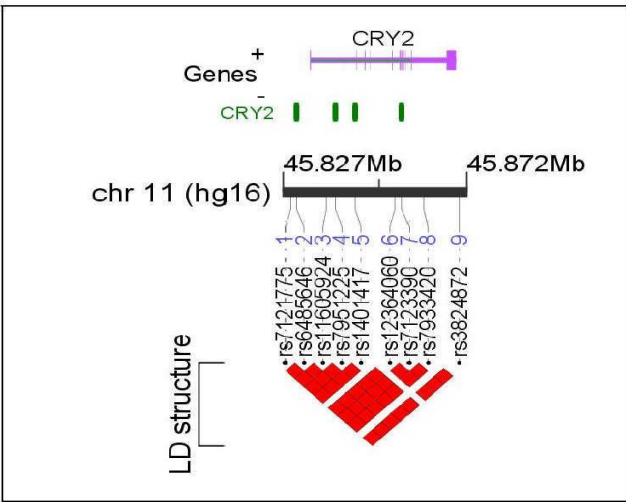


Type of file: figure

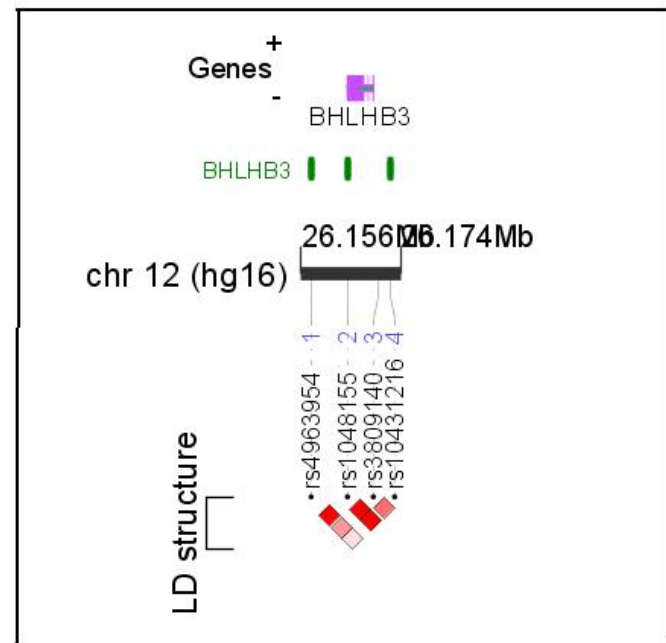
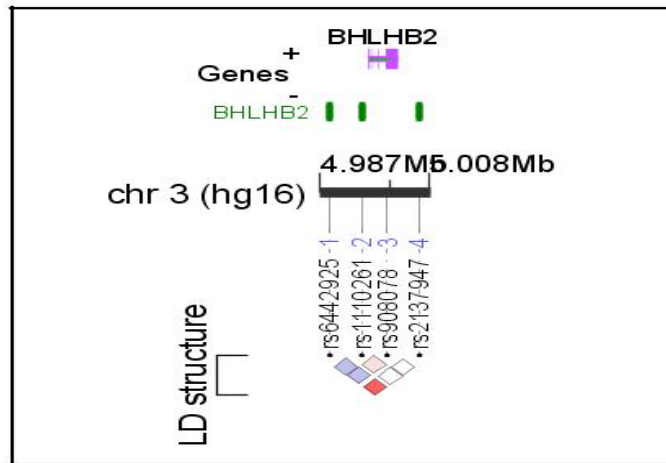
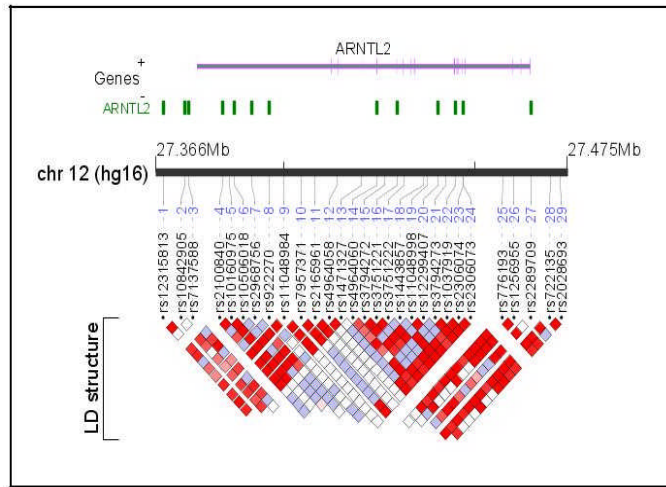
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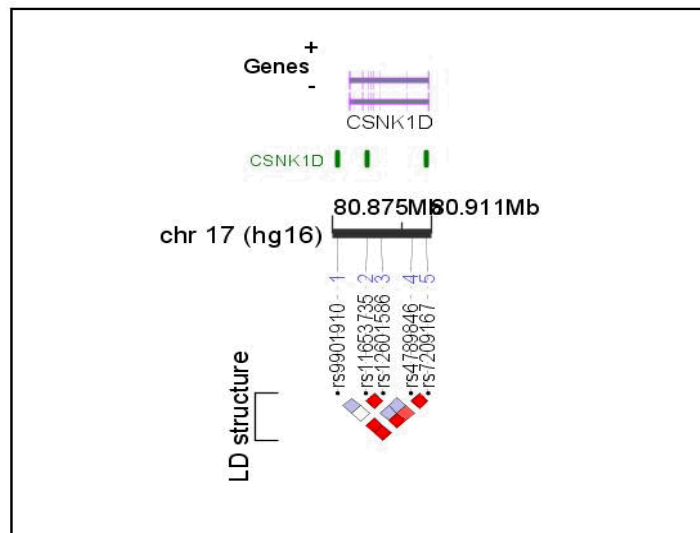
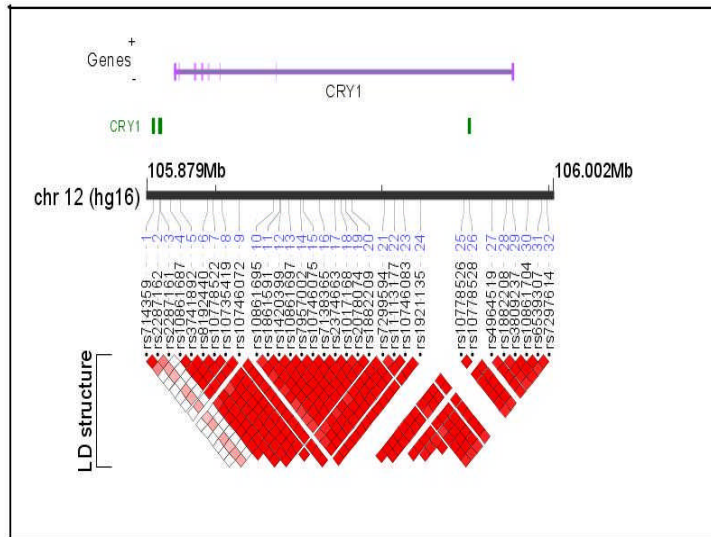
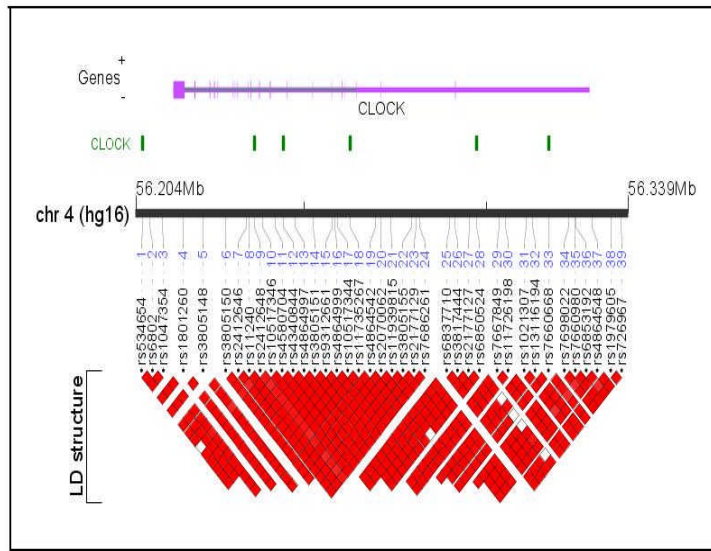
Filename: Supplementary Figure II LD plots.doc

**Supplementary Figure II.** Linkage Disequilibrium (LD) Plot at Each Circadian Gene Region. The LD structure was constructed using the genotype data of the 30 Centre d'Etude du Polymorphisme Humain (CEPH) trios in the International HapMap Project. The horizontal black line depicts the genomic region. The single nucleotide polymorphisms (SNPs) tested in this study and the structure of each gene, with vertical lines indicating exons, are shown above the chromosome bar in green and in lavender, respectively. SNPs with minor allele frequency  $\geq 0.1$  in the gene region are shown below the black chromosome line. A linkage disequilibrium plot is shown in the bottom part of the figure based on the measure  $D'$ : each square represents the magnitude of linkage disequilibrium for a single pair of SNPs, with red color indicating linkage disequilibrium that is strong ( $D' > 0.8$ ) and statistically significant (logarithm of odds  $> 2.0$ ), and white indicating  $D' < 0.5$ . This figure was prepared using the program LocusView 2.0 (T. Petryshen, A. Kirby, M. Ainscow, unpublished software; <http://www.broad.mit.edu/mpg/locusview>). Genomic positions are in accordance with the National Center for Biotechnology Information build 34 hg16 of the human genome assembly.

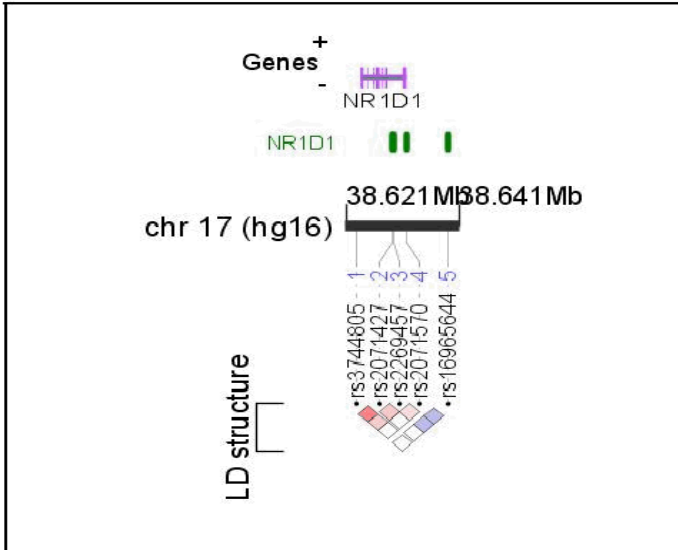
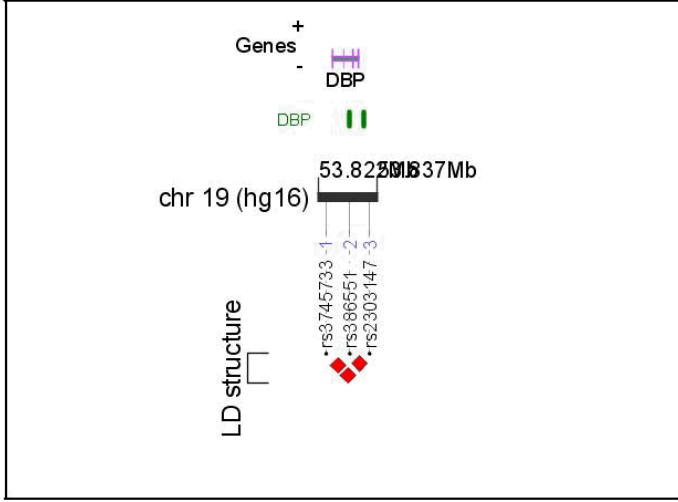
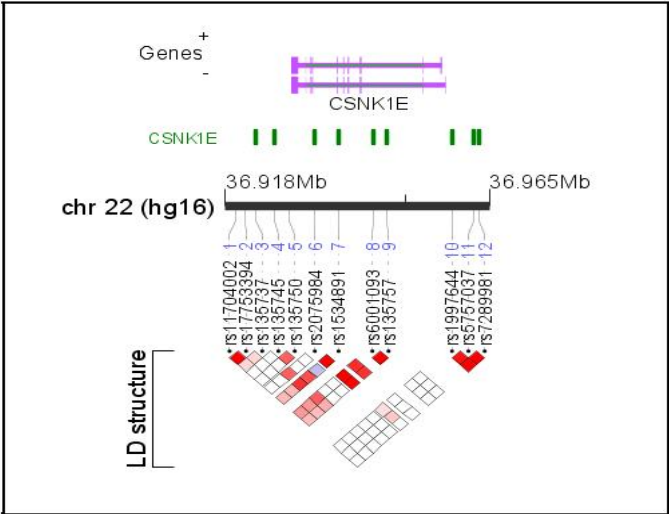












Type of file: table

Label: 5

Filename: Suppl Table I Altered Expression data in Stanley samples.doc

Supplementary Table I. Altered Expression of Circadian Genes in the Stanley Foundation Brain Collections of Bipolar Disorder

	Consortium collection <sup>a</sup>	Array collection <sup>b</sup>	Combined analysis
<i>ARNTL</i>	NS	-1.087 ( $p = 0.0319$ ) <sup>c</sup>	-1.107 ( $p = 0.0038$ )
<i>ARNTL2</i>	NS	NS	-1.05 ( $p = 0.018$ )
<i>BHLHB2</i>	NS	-1.196 ( $p = 0.0004$ )	-1.186 ( $p = 0.00016$ )
<i>NPAS2</i>	-1.097 ( $p = 0.0399$ )	NS	-1.05 ( $p = 0.0116$ )
<i>CLOCK</i>	NS	-1.047 ( $p = 0.0432$ )	NS
<i>CRY2</i>	NS	+1.066 ( $p = 0.0137$ )	NS

Data are presented as fold changes and  $p$ -values for difference between patients and controls. <sup>a</sup> The Neuropathology Consortium collection includes 15 patients with bipolar disorder (BP) and 15 unaffected controls. <sup>b</sup> The Stanley Array Collection includes 35 patients with BP and 35 unaffected controls. <sup>c</sup> Fold changes (+ and - indicate increased and decreased gene expression, respectively) have been adjusted for potential confounding variables such as postmortem interval, brain pH, age at death, sex, and severity of substance and/or alcohol abuse. Within each of 12 microarray studies, the probes including that for circadian genes are analyzed individually for association with BP. This produces a fold change and confidence interval for each probe/disease in each study. For each unique gene, these fold changes and confidence intervals are aggregated across probes and studies, giving a mean and confidence interval reflecting all of the study/probe specific data for that gene. The gene's consensus fold change is a weighted mean of the individual fold changes (weights =  $1/SE_i$ ), and the  $p$ -value is based on the t-statistic for the weighted fold change and combined standard error of the fold change. This cross study analysis is performed within the Array collection studies, within the Consortium collection studies, and across all studies (combined analysis). NS, not significant. Other circadian genes tested in our study do not show significant abnormal expression in Stanley bipolar disorder brain samples. For more information, please visit the website of the Stanley Medical Research Institute Online Genomics Database at <https://www.stanleygenomics.org/>. Unpublished data with permission from Drs Fuller Torrey and Michael Elashoff and the Stanley Medical Research Institute.

Type of file: table

Label: 6

Filename: Suppl Table II Results of sib\_tdt of 19 SNPs in sample i.doc

Supplementary Table II. Results of sib\_tdt Analyses of 19 SNPs of 5 Circadian Genes in CNG and NIMH Waves 1-2 Bipolar Disorder Families (Sample I)

Gene	SNP	Proportion allele 1 is transmitted	T	NT	TDT <i>P</i> -value*
<i>CRY2</i>	rs6485646	0.47	60	69	0.25
<i>CRY2</i>	rs7951225	0.55	47	38	0.07
<i>CRY2</i>	rs1401417	0.46	37	44	0.94
<i>CRY2</i>	rs7123390	0.51	44	43	1.00
<i>PER1</i>	rs6503086	0.53	52	47	0.79
<i>PER1</i>	rs2518023	0.62	23	14	0.51
<i>PER1</i>	rs2278637	0.53	46	40	0.39
<i>PER2</i>	rs10201361	0.33	2	4	1.00
<i>PER2</i>	rs2304674	0.55	48	40	0.49
<i>PER2</i>	rs2304672	0.58	18	13	0.38
<i>PER3</i>	rs228642	0.43	46	60	0.70
<i>PER3</i>	rs228644	0.56	60	47	0.55
<i>PER3</i>	rs228665	0.44	41	53	0.51
<i>PER3</i>	rs1150394	0.54	50	42	1.00
<i>PER3</i>	rs707472	0.62	43	26	0.25
<i>TIMELESS</i>	rs2291738 <sup>a</sup>	0.48	43	59	1.00
<i>TIMELESS</i>	rs774026 <sup>a</sup>	0.48	38	46	1.00
<i>TIMELESS</i>	rs2279665 <sup>a</sup>	0.46	40	52	0.39
<i>TIMELESS</i>	rs10876890 <sup>a</sup>	0.52	60	49	0.29

<sup>a</sup>rs2291738 and rs10876890 were found to be associated with insomnia during mania episode in bipolar disorder patients in CNG and waves 1-2 samples, then were genotyped in CHIP and waves 3-4 samples. SNPs rs774026 and rs2279665 were genotyped in CHIP, CNG, and NIMH waves 1-4 samples, as these two SNPs showed suggestive evidence of association with bipolar disorder (Mansour HA et al. *Genes Brain Behav.* 2006; 5:150-157). T and NT: numbers of allele1 transmitted and non-transmitted from heterozygous parents to affected offspring.

Type of file: table

Label: 7

Filename: Suppl Table III Haplotype Analysis in sample I.doc

Supplementary Table III. Haplotype Analysis of 19 SNPs in 5 Circadian Genes in the CNG and NIMH waves 1-2 samples (Sample I)

Haplotype	Frequency	<i>p</i> -value	q-value <sup>a</sup>
Block-1-Markers:rs228642,rs228644-11	0.03	0.12	0.84
Block-1-Markers:rs228642,rs228644-12	0.39	0.83	1.00
Block-1-Markers:rs228642,rs228644-21	0.42	0.44	0.84
Block-1-Markers:rs228642,rs228644-22	0.16	0.19	0.84
Block-2-Markers:rs228665,rs1150394,rs707472-111	0.33	0.67	0.96
Block-2-Markers:rs228665,rs1150394,rs707472-121	0.15	0.46	0.84
Block-2-Markers:rs228665,rs1150394,rs707472-122	0.15	0.44	0.84
Block-2-Markers:rs228665,rs1150394,rs707472-221	0.35	0.3	0.84
Block-3-Markers:rs6503086,rs2518023,rs2278637-112	0.38	0.99	1.00
Block-3-Markers:rs6503086,rs2518023,rs2278637-211	0.28	0.25	0.84
Block-3-Markers:rs6503086,rs2518023,rs2278637-212	0.23	0.33	0.84
Block-3-Markers:rs6503086,rs2518023,rs2278637-221	0.08	0.66	0.96
Block-4-Markers:rs6485646,rs7951225,rs1401417,rs7123390-1212	0.52	0.24	0.84
Block-4-Markers:rs6485646,rs7951225,rs1401417,rs7123390-2112	0.25	0.013	0.53
Block-4-Markers:rs6485646,rs7951225,rs1401417,rs7123390-2211	0.03	0.51	0.84
Block-4-Markers:rs6485646,rs7951225,rs1401417,rs7123390-2221	0.2	0.48	0.84
Block-5-Markers:rs774026,rs2279665,rs10876890-222 <sup>b</sup>	0.01	0.13	0.60
Block-5-Markers:rs774026,rs2279665,rs10876890-111 <sup>b</sup>	0.02	0.16	0.60
Block-5-Markers:rs774026,rs2279665,rs10876890-212 <sup>b</sup>	0.05	0.18	0.60
Block-5-Markers:rs774026,rs2279665,rs10876890-121 <sup>b</sup>	0.05	0.65	1.00
Block-5-Markers:rs774026,rs2279665,rs10876890-221 <sup>b</sup>	0.42	0.78	1.00
Block-5-Markers:rs774026,rs2279665,rs10876890-112 <sup>b</sup>	0.45	0.97	1.00
Block-6-Markers:rs10201361,rs2304674,rs2304672-212	0.72	0.49	0.84
Block-6-Markers:rs10201361,rs2304674,rs2304672-221	0.08	0.44	0.84
Block-6-Markers:rs10201361,rs2304674,rs2304672-222	0.18	0.99	1.00

<sup>a</sup>q values by false discovery rate (FDR) analysis. <sup>b</sup> rs2291738 and rs10876890 in *TIMELESS* were found to be associated with insomnia during mania episode in bipolar disorder patients in CNG and waves 1-2 samples, then were genotyped in CHIP and waves 3-4 samples. SNPs rs774026 and rs2279665 in *TIMELESS* were genotyped in CHIP, CNG, and NIMH waves 1-4 samples, as these two SNPs showed suggestive association evidence with bipolar disorder by Nimgaonkar's group (Mansour HA et al. Genes Brain Behav. 2006; 5:150-157). Thus, haplotype association data in *TIMELESS* (block 5) was based genotypes in CHIP, CNG, and NIMH waves 1-4 samples.

Type of file: table

Label: 8

Filename: Suppl Table IV sib\_tdt results of 62 SNPs in sample ii.doc



Supplementary Table IV. Results of sib\_tdt Analyses of 62 SNPs at 10 Circadian Genes in CNG, NIMH Waves 1-4, and CHIP Bipolar Disorder Families (Sample II)

Gene	SNP	Proportion allele 1 is transmitted	T	NT	TDT <i>p</i> -value*
<i>ARNTL</i>	rs900144	0.45	124	152	1
<i>ARNTL</i>	rs2279286	0.44	104	134	0.85
<i>ARNTL</i>	rs4146388	< 5 transmissions	0	0	1
<i>ARNTL</i>	rs4757142	0.44	114	148	0.94
<i>ARNTL</i>	rs4757144	0.46	125	149	0.91
<i>ARNTL</i>	rs10832022	0.44	93	117	0.59
<i>ARNTL</i>	rs6486121	0.48	131	143	0.71
<i>ARNTL</i>	rs12421530	0.49	134	141	1
<i>ARNTL</i>	rs3816360	0.50	135	135	0.62
<i>ARNTL</i>	rs3789327	0.50	132	132	0.82
<i>ARNTL</i>	rs11022778	0.51	127	121	0.81
<i>ARNTL</i>	rs2278749	0.48	83	90	0.96
<i>ARNTL</i>	rs969485	0.51	120	113	0.6
<i>ARNTL</i>	rs2290035	0.52	154	142	0.63
<i>ARNTL2</i>	rs12315813	0.51	97	93	1
<i>ARNTL2</i>	rs10842905	0.49	124	130	0.83
<i>ARNTL2</i>	rs7137588	0.50	129	131	0.83
<i>ARNTL2</i>	rs2100840	0.48	63	67	0.59
<i>ARNTL2</i>	rs10506018	0.52	77	72	0.56
<i>ARNTL2</i>	rs2968756	0.55	85	70	0.29
<i>ARNTL2</i>	rs922270	0.43	54	71	0.21
<i>ARNTL2</i>	rs4964060	0.48	127	137	0.3
<i>ARNTL2</i>	rs3751221	0.50	69	70	0.52
<i>ARNTL2</i>	rs12299407	0.43	43	56	0.3
<i>ARNTL2</i>	rs1037919	0.46	75	90	0.099
<i>ARNTL2</i>	rs2306074	0.52	125	116	0.65
<i>ARNTL2</i>	rs2289709	0.50	57	56	0.77
<i>BHLHB2</i>	rs6442925	0.61	90	57	0.062
<i>BHLHB2</i>	rs1110261	0.49	87	92	0.83
<i>BHLHB2</i>	rs908078	0.50	75	76	0.5
<i>BHLHB2</i>	rs2137947	0.44	76	95	0.21
<i>BHLHB3</i>	rs4963954	0.52	144	137	0.36
<i>BHLHB3</i>	rs1048155	0.50	157	160	0.88
<i>BHLHB3</i>	rs10431216	0.53	106	94	1
<i>CLOCK</i>	rs534654	0.40	82	122	0.0097
<i>CLOCK</i>	rs2412648	0.46	113	133	0.12
<i>CLOCK</i>	rs4340844	0.44	119	154	0.015
<i>CLOCK</i>	rs11735267	0.55	159	127	0.059

Gene	SNP	Proportion allele 1 is transmitted	T	NT	TDT <i>p</i> -value*
<i>CLOCK</i>	rs6850524	0.43	126	168	0.012
<i>CLOCK</i>	rs7660668	0.51	116	113	0.59
<i>CRY1</i>	rs714359	0.48	100	107	0.45
<i>CRY1</i>	rs2287162	0.49	113	116	0.47
<i>CRY1</i>	rs2287161	0.52	159	144	0.55
<i>CRY1</i>	rs10778528	0.51	144	141	0.73
<i>CSNK1D</i>	rs9901910	0.50	77	76	0.8
<i>CSNK1D</i>	rs11653735	0.54	91	77	0.87
<i>CSNK1D</i>	rs7209167	0.53	150	134	0.64
<i>CSNK1E</i>	rs135737	0.47	97	108	0.79
<i>CSNK1E</i>	rs135745	0.48	142	151	0.72
<i>CSNK1E</i>	rs2075984	0.54	159	134	0.35
<i>CSNK1E</i>	rs1534891	0.40	50	75	0.84
<i>CSNK1E</i>	rs6001093	0.53	92	82	0.82
<i>CSNK1E</i>	rs135757	0.44	94	121	0.95
<i>CSNK1E</i>	rs1997644	0.51	148	142	1
<i>CSNK1E</i>	rs5757037	0.51	134	129	0.6
<i>CSNK1E</i>	rs7289981	0.48	58	63	0.94
<i>DBP</i>	rs386551	0.51	111	108	0.51
<i>DBP</i>	rs3848543	0.45	65	78	0.71
<i>NR1D1</i>	rs2071427	0.49	118	123	0.52
<i>NR1D1</i>	rs2269457	0.55	121	98	0.72
<i>NR1D1</i>	rs2071570	0.44	92	118	1
<i>NR1D1</i>	rs16965644	0.47	67	74	0.93

\*Nominally significant *p*-values are highlighted in red. T and NT: numbers of allele1 transmitted and non-transmitted from heterozygous parents to affected offspring.

Type of file: table

Label: 9

Filename: Suppl Table V Haplotype Analysis in Samples II.doc

Supplementary Table V. Haplotype Analysis of 62 SNPs in 10 Circadian Genes in CNG, NIMH Waves 1-4 and CHIP Samples (Sample II)

Haplotype	Frequency	p-value	q-value <sup>a</sup>
Block-1-Markers:rs534654,rs2412648,rs4340844,rs11735267,rs6850524,rs7660668-111211	0.19	<b>0.034</b>	0.8
Block-1-Markers:rs534654,rs2412648,rs4340844,rs11735267,rs6850524,rs7660668-211112	0.04	<b>0.025</b>	0.79
Block-1-Markers:rs534654,rs2412648,rs4340844,rs11735267,rs6850524,rs7660668-211122	0.22	0.81	1
Block-1-Markers:rs534654,rs2412648,rs4340844,rs11735267,rs6850524,rs7660668-211211	0.15	0.94	1
Block-1-Markers:rs534654,rs2412648,rs4340844,rs11735267,rs6850524,rs7660668-212121	0.07	<b>0.028</b>	0.79
Block-1-Markers:rs534654,rs2412648,rs4340844,rs11735267,rs6850524,rs7660668-222121	0.31	0.069	0.97
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-11111	0.53	0.56	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-11121	0.01	0.23	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-11211	0.01	0.062	0.97
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-11221	0.01	0.23	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-11222	0.01	0.77	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-12111	0.01	0.14	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-21111	0.01	0.23	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-21211	0.01	0.58	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-21221	0.13	0.9	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-21222	0.01	0.079	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-22111	0.02	0.39	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-22122	0.01	0.85	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-22221	0.03	0.27	1
Block-2-Markers:rs900144,rs2279286,rs4757142,rs4757144,rs10832022-22222	0.19	0.7	1
Block-3-Markers:rs6486121,rs12421530,rs3816360-111	0.01	0.27	1
Block-3-Markers:rs6486121,rs12421530,rs3816360-112	0.6	0.99	1
Block-3-Markers:rs6486121,rs12421530,rs3816360-121	0.04	0.4	1
Block-3-Markers:rs6486121,rs12421530,rs3816360-212	0.01	0.99	1
Block-3-Markers:rs6486121,rs12421530,rs3816360-221	0.29	0.42	1
Block-3-Markers:rs6486121,rs12421530,rs3816360-222	0.05	0.26	1
Block-4-Markers:rs3789327,rs11022778-11	0.54	0.63	1
Block-4-Markers:rs3789327,rs11022778-21	0.13	0.33	1
Block-4-Markers:rs3789327,rs11022778-22	0.33	0.74	1
Block-5-Markers:rs2278749,rs969485,rs2290035-111	0.01	0.74	1
Block-5-Markers:rs2278749,rs969485,rs2290035-112	0.16	0.84	1
Block-5-Markers:rs2278749,rs969485,rs2290035-211	0.51	0.66	1
Block-5-Markers:rs2278749,rs969485,rs2290035-222	0.32	0.68	1
Block-6-Markers:rs4963954,rs1048155-11	0.55	0.62	1
Block-6-Markers:rs4963954,rs1048155-12	0.12	0.15	1
Block-6-Markers:rs4963954,rs1048155-22	0.33	0.6	1
Block-7-Markers:rs12315813,rs10842905,rs7137588,rs2100840,rs10506018-12111	0.11	0.37	1
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Block-7-Markers:rs12315813,rs10842905,rs7137588,rs2100840,rs10506018-21121	0.54	0.41	1
Block-7-Markers:rs12315813,rs10842905,rs7137588,rs2100840,rs10506018-21222	0.16	0.53	1
Block-7-Markers:rs12315813,rs10842905,rs7137588,rs2100840,rs10506018-22121	0.01	0.71	1
Block-7-Markers:rs12315813,rs10842905,rs7137588,rs2100840,rs10506018-22221	0.1	1	1

Block-8-Markers:rs2968756,rs922270-11	0.73	1	1
Block-8-Markers:rs2968756,rs922270-12	0.14	0.29	1
Block-8-Markers:rs2968756,rs922270-21	0.14	0.36	1
Block-9-Markers:rs4964060,rs3751221,rs12299407,rs1037919,rs2306074,rs2289709-111122	0.15	0.1	1
Block-9-Markers:rs4964060,rs3751221,rs12299407,rs1037919,rs2306074,rs2289709-111212	0.07	0.31	1
Block-9-Markers:rs4964060,rs3751221,rs12299407,rs1037919,rs2306074,rs2289709-121221	0.04	1	1
Block-9-Markers:rs4964060,rs3751221,rs12299407,rs1037919,rs2306074,rs2289709-122221	0.06	0.49	1
Block-9-Markers:rs4964060,rs3751221,rs12299407,rs1037919,rs2306074,rs2289709-122222	0.04	0.25	1
Block-9-Markers:rs4964060,rs3751221,rs12299407,rs1037919,rs2306074,rs2289709-211212	0.6	0.38	1
Block-10-Markers:rs714359,rs2287162-11	0.01	0.32	1
Block-10-Markers:rs714359,rs2287162-12	0.2	0.47	1
Block-10-Markers:rs714359,rs2287162-21	0.73	0.34	1
Block-10-Markers:rs714359,rs2287162-22	0.06	0.86	1
Block-11-Markers:rs2269457,rs2071570,rs16965644-111	0.08	0.4	1
Block-11-Markers:rs2269457,rs2071570,rs16965644-121	0.55	0.63	1
Block-11-Markers:rs2269457,rs2071570,rs16965644-122	0.14	0.75	1
Block-11-Markers:rs2269457,rs2071570,rs16965644-211	0.14	0.79	1
Block-11-Markers:rs2269457,rs2071570,rs16965644-221	0.1	0.44	1
Block-12-Markers:rs9901910,rs11653735,rs7209167-111	0.18	0.8	1
Block-12-Markers:rs9901910,rs11653735,rs7209167-121	0.26	0.62	1
Block-12-Markers:rs9901910,rs11653735,rs7209167-122	0.41	0.79	1
Block-12-Markers:rs9901910,rs11653735,rs7209167-222	0.15	1	1
Block-13-Markers:rs386551,rs3848543-12	0.73	0.55	1
Block-13-Markers:rs386551,rs3848543-21	0.14	0.75	1
Block-13-Markers:rs386551,rs3848543-22	0.13	0.28	1
Block-14-Markers:rs135745,rs2075984,rs1534891-112	0.22	0.45	1
Block-14-Markers:rs135745,rs2075984,rs1534891-121	0.1	0.97	1
Block-14-Markers:rs135745,rs2075984,rs1534891-122	0.13	0.43	1
Block-14-Markers:rs135745,rs2075984,rs1534891-212	0.27	0.31	1
Block-14-Markers:rs135745,rs2075984,rs1534891-221	0.01	0.3	1
Block-14-Markers:rs135745,rs2075984,rs1534891-222	0.26	0.26	1
Block-15-Markers:rs6001093,rs135757-11	0.06	0.26	1
Block-15-Markers:rs6001093,rs135757-12	0.75	1	1
Block-15-Markers:rs6001093,rs135757-21	0.19	0.56	1
Block-16-Markers:rs1997644,rs5757037,rs7289981-121	0.12	0.69	1
Block-16-Markers:rs1997644,rs5757037,rs7289981-122	0.41	0.58	1
Block-16-Markers:rs1997644,rs5757037,rs7289981-212	0.38	0.87	1
Block-16-Markers:rs1997644,rs5757037,rs7289981-222	0.09	0.45	1

<sup>a</sup> q-values by false discovery rate (FDR) analysis. *p*-values < 0.05 are shown in bold type.