

# CDH13 and HCRTR2 May Be Associated with Hypersomnia Symptom of Bipolar Depression: A Genome-Wide Functional Enrichment Pathway Analysis

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Although bipolar disorder is highly heritable, the identification of specific genetic variations is limited because of the complex traits underlying the disorder. We performed a genome-wide association study of bipolar disorder using a subphenotype that shows hypersomnia symptom during a major depressive episode. We investigated a total of 2,191 cases, 1,434 controls, and 703,012 single nucleotide polymorphisms (SNPs) in the merged samples obtained from the Translational Genomics Institute and the Genetic Association Information Network. The gene emerging as the most significant by statistical analysis was rs1553441 (odds ratio=0.4093;  $p=1.20 \times 10^{-5}$ ; Permuted  $p=6.0 \times 10^{-6}$ ). However, the  $5 \times 10^{-8}$  threshold for statistical significance required in a genome-wide association study was not achieved. The functional enrichment pathway analysis showed significant enrichments in the adhesion, development-related, synaptic transmission-related, and cell recognition-related pathways. For further evaluation, each gene of the enriched pathways was reviewed and matched with genes that were suggested to be associated with psychiatric disorders by previous genetic studies. We found that the cadherin 13 and hypocretin (orexin) receptor 2 genes may be involved in the hypersomnia symptom during a major depressive episode of bipolar disorder.

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**Key Words** Genome-wide association study, Bipolar disorder, Hypersomnia, Functional enrichment pathway analysis, Bipolar depression.

## INTRODUCTION

Bipolar disorder (BD) patients suffer from both a low physical quality and low mental quality of life, even during an euthymic period.<sup>1</sup> BD is known to be highly heritable; however, the identification of specific genetic variations resulted in limited findings.<sup>2,3</sup> One reason for this low success rate in identifying genetic variations relies in the nature and complex traits of BD.<sup>4</sup> As a consequence, dividing BD into subgroups according to clinical subphenotypes is a reliable alternative ap-

proach for future genetic studies in BD.<sup>5</sup>

Several studies suggested that dysregulation of the circadian rhythm is associated with the pathophysiology of BD.<sup>6,7</sup> In general, BD patients have common specific circadian rhythm-related clinical manifestations such as: diurnal mood variation, periodicity of manic-depressive episodes, activity changes, alteration of the secretion of hormones and other endogenous substances, and sleep disturbances.<sup>8-10</sup> Sleep disturbances may have a negative effect on emotional regulation.<sup>11</sup> According to these results, it can be assumed that circadian rhythm dysregulation is very closely associated with BD.<sup>12</sup>

We hypothesized that a subphenotype group that shows hypersomnia symptom during a major depressive episode of bipolar disorder may represent a genetically distinct subtype of BD. We tested this hypothesis using a genome-wide association (GWA) analysis between subjects that showed hypersomnia symptom during a major depressive episode of bipolar disorder (hypersomnia symptom of bipolar depression,

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HBD) and subjects that did not show hypersomnia symptom during a major depressive episode of bipolar disorder (non-hypersomnia symptom of bipolar depression, NHBD). The subject samples were of European ancestry and were genotyped as part of the Genetic Association Information Network (GAIN) by the Bipolar Genome Study (BiGS).

## METHODS

### Subject ascertainment

Prior to genotyping, which was part of the BiGS, the unrelated bipolar I disorder subjects of European ancestry were selected from those collected by the National Institute of Mental Health Genetics Initiative for Bipolar Disorder. All subjects provided written informed consent in accordance to protocols from local institutional review boards. The subjects were interviewed using protocols from the Diagnostic Interview for Genetic Studies (DIGS).<sup>13</sup> Information was obtained from family informants and medical records. The information was reviewed along with the interview by a panel of experienced clinicians to obtain a final best-estimate diagnosis. Control subjects were selected after they were certified through a National Institute of Mental Health-supported contract between Dr. Pablo Gejman and Knowledge Networks, Inc.<sup>14</sup> All subjects donated a blood sample and were given medical questionnaires. The selected controls were matched for gender and ethnicity with the BD cases. Control subjects who had a history of BD, psychosis, or recurrent major depression were excluded from our study. The subject samples as part of the GAIN were obtained by Dr. Kelsoe who is a member of the BiGS.

### Genotyping and cleaning

The first set of samples was genotyped at the Broad Institute, as part of GAIN, using the Affymetrix SNP Array 6.0 (Affymetrix; Santa Clara, CA, US) 1M SNP array. We obtained a total of 1,001 BD cases, 1,033 controls, and 724,067 single nucleotide polymorphisms (SNPs). These were available for analysis following an extensive quality control (QC) process.<sup>15</sup> The QC process eliminated all individuals with >10% missing data, SNPs with poor allele clustering, duplicate errors, minor allele frequencies <0.05, and significant deviation from Hardy-Weinberg equilibrium at  $p < 10^{-6}$ . The second set of samples was genotyped similarly to the first set of samples at the Translational Genomics Institute (TGEN) and underwent a comparable QC. From this set of samples we obtained 1,190 BD cases, 401 controls, and 728,187 SNPs available for analysis. An additional round of QC was performed on the merged samples from GAIN and TGEN. This merge resulted in a set of 703,012 SNPs that passed the imposed QC process.

### Phenotypes

As part of the DIGS interview, bipolar I disorder subjects were queried as to whether they had a hypersomnia symptom during major depressive episodes. According to the answer, subjects were categorized either into the HBD or the NHBD group. Those who answered 'Unknown' to the question about hypersomnia symptom were categorized as the missing group. After filtering, there were 263 BD subjects in the HBD group and 112 subjects in the NHBD group.

### Association analyses

To assess genetic factors contributing to HBD, we performed a genome-wide case-only analysis of HBD versus NHBD. This association analysis was performed using a logistic regression using PLINK<sup>16</sup> with a covariance adjustment for sex and age. Adaptive permutations were performed to find the empirical significance of the results using PLINK.<sup>16</sup>

### SNP imputation

Missing SNPs were imputed using the IMPUTE2 tool<sup>17</sup> and the CEU panel of HapMap 3+1,000 Genomes Pilot haplotypes as a reference. The imputed SNPs were used for the functional enrichment pathway analysis.

### Functional enrichment pathway analysis

Gene ontology analysis was performed on the gene sets harboring the identified SNPs ( $p < 0.005$ ) evaluated using the DAVID software.<sup>18,19</sup> The enriched gene functions were identified from the HBD versus NHBD analysis using an enrichment score. To go further in our investigation, we made a list of genes of the enriched pathways and compared them with various genes that were suggested to be related to psychiatric disorders by previous genetic studies. We searched the available databases in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and in the National Human Genome Research Institute (<http://www.genome.gov/>) for genes of enriched pathways. Some of the search terms included: the name of each gene of enriched pathways and "psychiatric disorder or depression or bipolar disorder or schizophrenia or circadian rhythm". After the review and matching, we selected genes from those of enriched pathways that were described as susceptible genes in psychiatric disorders by previous genetic studies.

## RESULTS

Eighty associated SNPs with  $p < 10^{-4}$  were identified in this present genome-wide case-only analysis. We found that rs1553441 is the gene that appeared to be the most significant after statistical analysis (odds ratio=0.4093,  $p$  value of  $1.20 \times 10^{-5}$ , Permuted  $p=6.0 \times 10^{-6}$ ) (Supplementary Figure 1 in the online-

only Data Supplement). This SNP is located within a region of the gene encoding the phospholipase D family, member 5 (PLD5) on chromosome 1q43. However, the most significant gene of this study did not reach the p value of  $5 \times 10^{-8}$ , which is the threshold for statistical significance in a GWA.<sup>16</sup>

To determine whether the associated SNPs showed enrichment in certain functional pathways, we performed a genome-wide functional enrichment pathway analysis using the imputed data. Gene ontology functions were identified for all genes that contained SNPs associated with a significance level of  $p < 0.005$ . The functional enrichment analysis of HBD versus NHBD showed a significant enrichment of the adhesion, development-related, synaptic transmission-related, and cell recognition-related pathways (Supplementary Table 1 in the online-only Data Supplement). We can speculate that the altered functions of these pathways may contribute to the development of hypersomnia symptom during a major depressive episode of BP.

We aimed to investigate the genes of the enriched pathways in more detail. At first, we reviewed the results of previous genetic studies of psychiatric disorders found in the PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed/>) and the database from the National Human Genome Research Institute (<http://www.genome.gov/>). To search the databases we used search terms such as: the name of each gene of enriched pathways and “psychiatric disorder or major depressive disorder or bipolar disorder or schizophrenia or circadian rhythm”. In accordance with previously reported genetic findings, we investigated the significant genes of those identified from cate-

gories that showed significant enrichment by comparison to the results of previous genetic studies. We selected the genes of enriched pathways that matched those that have been suggested in the literature to be related to psychiatric disorders (Table 1). We ultimately found two matching genes: cadherin 13 (*CDH13*) and hypocretin (orexin) receptor 2 (*HCRTR2*). *CDH13* is located in 16q24.2 and encodes a member of the cadherin superfamily. The encoded protein acts as a negative regulator of axon growth during neural differentiation.<sup>20,21</sup> In the present pathway analysis, *CDH13* was identified as a member of genes thought to be involved in cell adhesion, biological adhesion, cell-cell adhesion, cell projection organization, and cell motion. *HCRTR2* is located in 6p12 and encodes a G protein-coupled receptor involved in regulation of feeding and sleep behavior.<sup>22</sup> In the present pathway analysis, *HCRTR2* was identified as a member of genes thought to be involved in cell-cell signaling, synaptic transmission, transmission of nerve impulse, and neurological system process.

## DISCUSSION

We were not able to identify significant genes in a GWA study that evaluated HBD versus NHBD. As a consequence, we focused on the pathways identified in genome-wide functional enrichment pathway analysis that showed significant enriched function. Specifically, we evaluated the gene lists of these enriched pathways, and compared them with genes that were previously suggested in the literature to be related to psychiatric disorders. This procedure was found to be helpful in find-

**Table 1.** Enrichment findings of the genome-wide functional enrichment pathway analysis in hypersomnia symptom of bipolar depression

Annotation cluster 1		Enrichment score: 6.7143
Term	p-value	Gene of interest
GO:0007155 cell adhesion	$1.96 \times 10^{-9}$	<i>CDH13</i>
GO:0022610 biological adhesion	$2.04 \times 10^{-9}$	<i>CDH13</i>
GO:0016337 cell-cell adhesion	0.0018	<i>CDH13</i>
Annotation cluster 2		Enrichment score: 4.0558
Term	p-value	Gene of interest
GO:0030030 cell projection organization	$6.83 \times 10^{-5}$	<i>CDH13</i>
GO:0006928 cell motion	0.0019	<i>CDH13</i>
Annotation cluster 3		Enrichment score: 3.2072
Term	p-value	Gene of interest
GO:0007267 cell-cell signaling	$1.15 \times 10^{-5}$	<i>HCRTR2</i>
GO:0007268 synaptic transmission	$3.82 \times 10^{-5}$	<i>HCRTR2</i>
GO:0019226 transmission of nerve impulse	$6.47 \times 10^{-4}$	<i>HCRTR2</i>
GO:0050877 neurological system process	0.5221	<i>HCRTR2</i>

A gene of interest is the result of a matching procedure based on previous genetic studies on psychiatric disorders. There were various genes identified as enriched genes of interest; however, we omitted all genes that did not overlap with the genetic findings from previously reported psychiatric genetic studies. Genes of annotation cluster 4 did not contain any genes that overlapped with previous studies, and was therefore omitted from this table. Supplementary Table 1 lists the full version of these results

ing genes that are possibly related to HBD, although this is an unfamiliar method and the results do not always provide an explanation on how genes are related.

*CDH13* is highly expressed in various brain regions such as the cerebral cortex, medulla, thalamus, and midbrain.<sup>20</sup> It has been suggested that *CDH13* is associated with various drug abuse-related phenotypes,<sup>23-28</sup> especially with respect to comorbid depression and alcohol dependence.<sup>29</sup> Disorders related to substance use, particularly alcohol dependence, show high comorbidity with BD.<sup>30</sup> In addition, the presence of substance abuse disorders seriously affects the course and prognosis of BD.<sup>31</sup> *CDH13* expression also showed an association with adiponectin levels<sup>32,33</sup> and depression.<sup>34</sup> Previous studies investigated adult depressed patients that showed decreased circulating levels of adiponectin.<sup>35-37</sup> One explanation for this finding could be that adiponectin is related to the Hypothalamic-Pituitary-Adrenal (HPA) axis. Several studies suggested a correlation between adiponectin and stress and development of various psychiatric disorders.<sup>38</sup> Furthermore, TNF- $\alpha$ , IL-10, and IL-6, previously shown to be regulated by adiponectin, also showed a correlation with BD.<sup>39,40</sup> TNF- $\alpha$  is suggested to produce an increased slow-wave sleep and a symptom of sleepiness.<sup>41</sup> Orexin, also known as hypocretin-A and B, neuromodulatory peptides secreted from orexin neurons, signal through orexin receptor 1 and orexin receptor 2 (*HCRTR1* and *HCRTR2*), which are G protein-coupled receptors.<sup>42</sup> Orexin-containing neurons project out to various monoaminergic nuclei of the brain, including the locus coeruleus (norepinephrine), the raphe nuclei (5-hydroxytryptamine, 5-HT), and the ventral tegmental area (dopamine). Therefore, the orexin-containing neurons can modify the monoaminergic neurons.<sup>43</sup> Furthermore, the presence of a functional positive feedback loop between the orexin and monoaminergic neurons has been suggested.<sup>44</sup> Orexin is implicated in diverse functions such as feeding, drinking, the sleep-wake cycle, hormone secretion, autonomic function, drug addiction, and reward. To date, most research has focused on the role of orexin in depression compared to other mood disorders, and several studies suggested that orexin plays a significant role in depression.<sup>45</sup> In particular, several studies have reported a role for orexin in sleep disturbance,<sup>46,47</sup> reward system,<sup>48</sup> feeding behavior,<sup>49,50</sup> hippocampal neuronal plasticity,<sup>51-53</sup> and monoamines.<sup>54,55</sup> It is important to note that BP is an important portion of depressive symptoms. Moreover, atypical depressive symptoms, characterized by hypersomnia, hyperphagia (or weight gain), and leaden paralysis, are more common in patients with BP than unipolar depression.<sup>56</sup> We speculate that representative symptoms of atypical depression, such as hypersomnia and hyperphagia, may be closely related to orexin's function. Moreover, a balanced effect of orexin's action on either the *HCRTR1*

or the *HCRTR2* receptor is important in achieving an anti-depressant- or pro-depressant-like effect.<sup>57</sup> Taken together, these previous findings suggest that hypersomnia symptoms during a major depressive episode of bipolar disorder are related to the functions of *CDH13* and *HCRTR2*.

We have explored the genetic association of BD using the HBD subphenotype to focus on a more homogenous group of subjects that present similar clinical courses. Although the present GWA of HBD versus NHBD did not produce significant results, the functional enrichment pathway analysis identified significant enrichments of the adhesion, development-related, synaptic transmission-related, and cell recognition-related pathways. In addition, we found that *CDH13* and *HCRTR2* show a potential correlation with HBD and we used a matching process based on the results of previous genetic studies performed on psychiatric disorders. To date, only several studies have been reported about this correlation. In the future, more studies focusing on the correlation between these pathways or several genes and HBD are needed to validate the results reported in the present study.

#### Supplementary Materials

The online-only Data Supplement is available with this article at <http://dx.doi.org/10.4306/pi.2015.12.3.402>.

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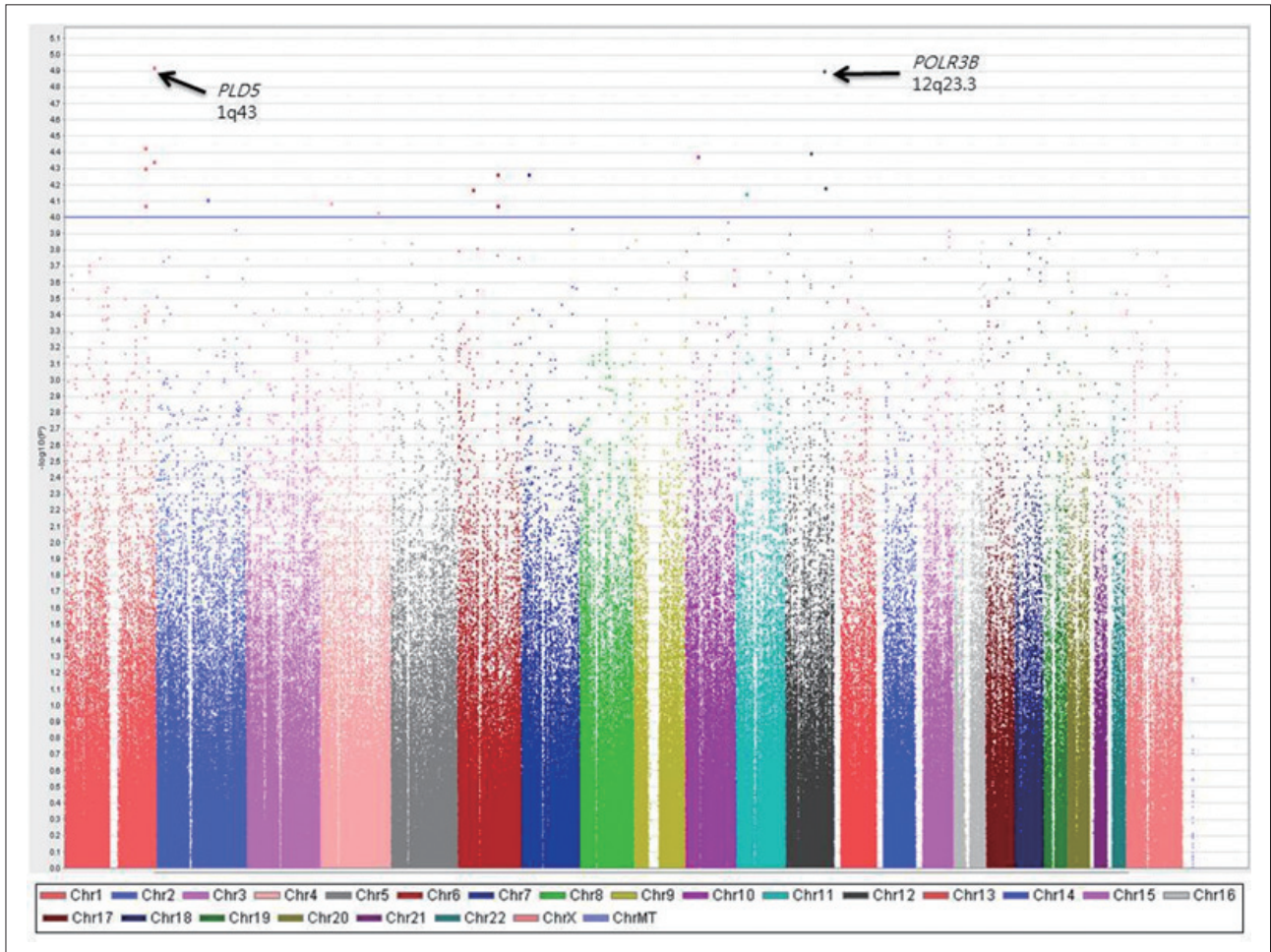
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**Supplementary Figure 1.** Genome-wide association results for hypersomnia bipolar depression. The Manhattan plot shows the results of susceptible loci relevant to hypersomnia bipolar depression. The chromosomal position is shown along the X-axis, whereas the  $-\log(p)$  value for each single nucleotide polymorphism is shown along the Y-axis. The horizontal line indicates the  $p < 10^{-4}$  significance threshold. The arrows in the figure indicate the position of possible relevant genes above the set threshold.

**Supplementary Table 1.** Enrichment findings from the genome-wide functional enrichment pathway analysis of hypersomnia bipolar depression

Annotation cluster 1		Enrichment score: 6.7143
Term	p-value	Genes
GO:0007155 cell adhesion	1.96×10 <sup>-9</sup>	<b>CDH13</b> , <i>DLC1, NRP2, MTSS1, NRP1, TLN2, NELL1, CD96, CDH20, DGCR2, DAB1, CHST10, NEGR1, SYK, DLG1, PTPRM, MAGI1, CNTNAP4, CNTN5, PCDH11Y, CNTNAP5, COL22A1, CDHR3, SIGLEC10, PCDH9, CHST4, PTPRT, CTNNA3, HES1, NCAM2, ARVCF, SIRPG, LAMC3, CNTN4, RELN, CNTN3, LAMC1, SEMA4D, ADAM12, CLDN16, PLXNC1, DSCAML1, NEDD9, OTOR, ITGB1, ITGBL1, SEMA5A, FAT4, ITGB8, PVRL3, COL6A3, COL8A1, COL18A1, HAPLN1, GMDS, LPP, CD99, NID2, RAPH1, PCDH19, LAMA4, ITGA8, CYFIP2, DSC1, FCGBP, PDZD2, NTM, CDH11, MUC16</i>
GO:0022610 biological adhesion	2.04×10 <sup>-9</sup>	<b>CDH13</b> , <i>DLC1, NRP2, MTSS1, NRP1, TLN2, NELL1, CD96, CDH20, DGCR2, DAB1, CHST10, NEGR1, SYK, DLG1, PTPRM, MAGI1, CNTNAP4, CNTN5, PCDH11Y, CNTNAP5, COL22A1, CDHR3, SIGLEC10, PCDH9, CHST4, PTPRT, CTNNA3, HES1, NCAM2, ARVCF, SIRPG, LAMC3, CNTN4, RELN, CNTN3, LAMC1, SEMA4D, ADAM12, CLDN16, PLXNC1, DSCAML1, NEDD9, OTOR, ITGB1, ITGBL1, SEMA5A, FAT4, ITGB8, PVRL3, COL6A3, COL8A1, COL18A1, HAPLN1, GMDS, LPP, CD99, NID2, RAPH1, PCDH19, LAMA4, ITGA8, CYFIP2, DSC1, FCGBP, PDZD2, NTM, CDH11, MUC16</i>
GO:0016337 cell-cell adhesion	0.0018	<b>CDH13</b> , <i>CLDN16, DSCAML1, OTOR, ITGB1, CDH20, DAB1, FAT4, PVRL3, DLG1, SYK, PTPRM, GMDS, PCDH11Y, CDHR3, PCDH9, PTPRT, CTNNA3, PCDH19, NCAM2, ITGA8, CYFIP2, CNTN4, DSC1, CDH11</i>
Annotation Cluster 2		Enrichment Score: 4.0558
Term	p-value	Genes
GO:0032989 cellular component morphogenesis	1.96×10 <sup>-6</sup>	<i>NRP2, NRP1, TFCP2L1, DSCAML1, GLI2, TTN, ITGB1, RAB3IP, SEMA5A, ATP2B2, IGF1R, CRYGB, SLC1A3, ANK1, DMD, CLASPI, UNC5C, SEMA3A, ROBO3, DLG1, COL18A1, NOX4, KLF7, PTPRM, CRYAA, RXRA, RTN4R, MYH6, HGF, WWTR1, NTN1, HES1, NCAM2, EPHA4, RELN, CNTN4, LAMC1, BMP7, SLITRK6, APBB2, GAP43</i>
GO:0000904 cell morphogenesis involved in differentiation	2.09×10 <sup>-6</sup>	<i>NRP2, NRP1, DSCAML1, GLI2, SEMA5A, ATP2B2, CRYGB, IGF1R, SLC1A3, SEMA3A, UNC5C, ROBO3, COL18A1, KLF7, PTPRM, CRYAA, RXRA, RTN4R, HGF, NTN1, HES1, EPHA4, NCAM2, RELN, CNTN4, LAMC1, BMP7, SLITRK6, APBB2, GAP43</i>
GO:0000902 cell morphogenesis	2.30×10 <sup>-6</sup>	<i>NRP2, NRP1, TFCP2L1, DSCAML1, GLI2, RAB3IP, SEMA5A, ATP2B2, IGF1R, CRYGB, SLC1A3, ANK1, DMD, CLASPI, UNC5C, SEMA3A, ROBO3, DLG1, COL18A1, NOX4, KLF7, PTPRM, CRYAA, RXRA, RTN4R, HGF, WWTR1, NTN1, HES1, NCAM2, EPHA4, RELN, CNTN4, LAMC1, BMP7, SLITRK6, APBB2, GAP43</i>
GO:0048667 cell morphogenesis involved in neuron differentiation	2.80×10 <sup>-5</sup>	<i>NRP2, NRP1, DSCAML1, GLI2, SEMA5A, IGF1R, ATP2B2, SLC1A3, ROBO3, SEMA3A, UNC5C, KLF7, PTPRM, RXRA, RTN4R, NTN1, HES1, EPHA4, NCAM2, CNTN4, RELN, BMP7, SLITRK6, APBB2, GAP43</i>
GO:0030030 cell projection organization	6.83×10 <sup>-5</sup>	<b>CDH13</b> , <i>NRP2, MTSS1, NRP1, DSCAML1, GLI2, RAB3IP, KLHL1, SPAG16, SEMA5A, ATP2B2, IGF1R, DMD, UNC5C, SEMA3A, ROBO3, FGD5, KLF7, GNAO1, PTPRM, RXRA, RTN4R, WWTR1, NTN1, EPHA4, NCAM2, NCK1, ITGA8, TSGA10, RELN, CNTN4, BMP7, SLITRK6, APBB2, GAP43</i>
GO:0007411 axon guidance	9.60 ×10 <sup>-5</sup>	<i>NRP2, KLF7, NRP1, PTPRM, GLI2, NTN1, SEMA5A, EPHA4, RELN, CNTN4, SEMA3A, ROBO3, UNC5C, APBB2, BMP7, GAP43</i>
GO:0048666 neuron development	1.71×10 <sup>-4</sup>	<i>NRP2, NRP1, DSCAML1, GLI2, KLHL1, SEMA5A, ATP2B2, IGF1R, SLC1A3, DMD, UNC5C, SEMA3A, ROBO3, KLF7, GNAO1, PTPRM, RXRA, NTN4, RTN4R, FIG4, NTN1, HES1, EPHA4, NCAM2, NTRK2, RELN, CNTN4, BMP7, SLITRK6, APBB2, GAP43, NTM</i>
GO:0007409 axonogenesis	1.88×10 <sup>-4</sup>	<i>NRP2, KLF7, NRP1, PTPRM, RXRA, RTN4R, DSCAML1, GLI2, NTN1, SEMA5A, EPHA4, NCAM2, IGF1R, CNTN4, RELN, SEMA3A, ROBO3, UNC5C, BMP7, APBB2, SLITRK6, GAP43</i>



**Supplementary Table 1.** Enrichment findings from the genome-wide functional enrichment pathway analysis of hypersomnia bipolar depression (continued)

GO:0048812	2.82×10 <sup>-4</sup>	<i>NRP2, KLF7, NRP1, PTPRM, RXRA, RTN4R, DSCAML1, GLI2, NTN1, SEMA5A, EPHA4, NCAM2, IGF1R, DMD, CNTN4, RELN, SEMA3A, UNC5C, ROBO3, BMP7, APBB2, SLITRK6, GAP43</i>
GO:0048858	3.35×10 <sup>-4</sup>	<i>NRP2, NRP1, DSCAML1, GLI2, RAB3IP, SEMA5A, IGF1R, DMD, SEMA3A, UNC5C, ROBO3, KLF7, PTPRM, RXRA, RTN4R, WWTR1, NTN1, EPHA4, NCAM2, CNTN4, RELN, BMP7, SLITRK6, APBB2, GAP43</i>
GO:0030182	4.24×10 <sup>-4</sup>	<i>NRP2, NRP1, DSCAML1, GLI2, KLHL1, SEMA5A, ATP2B2, IGF1R, SLC1A3, LHX1, DMD, UNC5C, SEMA3A, ROBO3, KLF7, GNAO1, PTPRM, MDGA1, RXRA, NTN4, RTN4R, VSX2, FIG4, NTN1, HES1, EPHA4, NCAM2, NTRK2, RELN, ID4, CNTN4, BMP7, SLITRK6, APBB2, CLN8, NTM, GAP43</i>
GO:0031175	6.34×10 <sup>-4</sup>	<i>NRP2, NRP1, DSCAML1, GLI2, KLHL1, SEMA5A, IGF1R, DMD, ROBO3, SEMA3A, UNC5C, KLF7, PTPRM, GNAO1, RXRA, RTN4R, NTN1, EPHA4, NCAM2, CNTN4, RELN, BMP7, SLITRK6, APBB2, GAP43</i>
GO:0032990	6.34×10 <sup>-4</sup>	<i>NRP2, NRP1, DSCAML1, GLI2, RAB3IP, SEMA5A, IGF1R, DMD, SEMA3A, UNC5C, ROBO3, KLF7, PTPRM, RXRA, RTN4R, WWTR1, NTN1, EPHA4, NCAM2, CNTN4, RELN, BMP7, SLITRK6, APBB2, GAP43</i>
GO:0006928	0.0019	<b><u>CDH13</u></b> , <i>NRP2, DNAH11, MTSS1, NRP1, FUT8, PLXNA2, CALD1, ABI3, MYLIP, GLI2, ITGB1, SEMA5A, DAB1, UNC5C, SEMA3A, ROBO3, SYK, KLF7, PTPRM, MDGA1, CHST4, NTN1, KDR, LSP1, EPHA4, IGSF8, TNS1, ETS1, BTG1, NCK1, RELN, CNTN4, LAMC1, BMP7, APBB2, GAP43</i>
Annotation Cluster 3		Enrichment Score: 3.2072
Term	p-value	Genes
GO:0007267	1.15×10 <sup>-5</sup>	<b><u>HCRTR2</u></b> , <i>SYT1, HNF1B, NRP1, GABRB3, GLRA1, SLC6A2, FGF14, GRIK4, FGF12, GLI2, GJA5, SLC1A3, WNT3, GRIN2B, SLC22A3, FRS2, SYK, CLN3, GABRG3, NPBWRI, CHST4, GRB10, SIRPG, SSTR1, HTR7, GRM7, WNT9B, ABAT, UNC13C, CLN8, SEMA5A, LHX1, DMD, PPP3CA, SLC30A8, PCSK5, NOS1, GABRA5, HGF, PARK2, ACCN1, PNOC, GRIA1, KCNN3, NTRK2, CACNA1E, RIT2, XCL1, GHSR, CACNA1B, HTR2A</i>
GO:0007268	3.82×10 <sup>-5</sup>	<b><u>HCRTR2</u></b> , <i>SYT1, GABRB3, GLRA1, SLC6A2, GRIK4, SLC1A3, GRIN2B, DMD, SLC22A3, PPP3CA, CLN3, GABRG3, NOS1, NPBWRI, GABRA5, PARK2, ACCN1, PNOC, GRIA1, KCNN3, GRM7, HTR7, ABAT, CACNA1E, RIT2, UNC13C, GHSR, CLN8, HTR2A, CACNA1B</i>
GO:0019226	6.47×10 <sup>-4</sup>	<b><u>HCRTR2</u></b> , <i>SYT1, GABRB3, GLRA1, SLC6A2, GRIK4, SLC1A3, GRIN2B, DMD, SLC22A3, PPP3CA, CLN3, GABRG3, NOS1, NPBWRI, GABRA5, PARK2, ACCN1, PNOC, GRIA1, KCNN3, GRM7, HTR7, ABAT, CACNA1E, RIT2, UNC13C, GHSR, CLN8, HTR2A, CACNA1B</i>
GO:0050877	0.5221	<b><u>HCRTR2</u></b> , <i>RP1, SYT1, OR1J2, GABRB3, GLRA1, OR4F21, SLC6A2, GRIK4, OR1N2, SOBP, ATP2B2, CRYGB, AGTR2, SLC1A3, CHST10, GRIN2B, SLC22A3, CHRNA7, KCNQ1, CLN3, OR52B2, GABRG3, CRYAA, CNTN5, NPBWRI, UBR3, NCAM2, HTR7, OTOF, GRM7, ABAT, UNC13C, CLN8, OTOR, PDE1C, DMD, PPP3CA, RLBP1, COL18A1, NOS1, GABRA5, PARK2, VSX2, ACCN1, CHML, PNOC, GRIA1, ITGA8, KCNN3, CACNA1E, RIT2, GHSR, VLDLR, CACNA1B, HTR2A</i>
Annotation Cluster 4		Enrichment Score: 2.4073
Term	p-value	Genes
GO:0008038	0.0021	<i>NCAM2, NRP1, CNTN4, SEMA3A, GAP43, NTM</i>
GO:0008037	0.0032	<i>CSGALNACT1, NCAM2, NRP1, COLEC12, CNTN4, FCGBP, SEMA3A, GAP43, NTM</i>
GO:0007413	0.0088	<i>NCAM2, NRP1, CNTN4, SEMA3A</i>

The genes matched to the results reported in previous genetic studies of psychiatric disorders are emphasized in this table in bold and underlined