

## **Replication BPD Sample Information**

Among all the tested European samples, both BPD patients and healthy controls provided written informed consent prior to their inclusion in the respective studies. All protocols used in the original studies reporting these samples were approved by the relevant ethical review bodies, and followed all applicable institutional, national and international guidelines.

### **Romania sample**

The Romania sample consisted of 380 BPD patients and 223 healthy controls. All patients were recruited from consecutive hospital admissions and directly interviewed with the Structured Clinical Interview for DSM-IV-TR-Axis I Disorders - Patient Version (SCID-I, 1994) and the Diagnostic Interview for Genetic Studies (DIGS) version 3.0 (1999). Information provided by medical records and interviews of family members was also used in a best estimate procedure of diagnosis on the basis of DSM-IV-TR criteria. The control sample was population-based, drawn from the same population as the patients, and was screened for major psychiatric disorders prior to inclusion. The ethnicity of the patients and control subjects was determined by genealogical investigation to the grandparental generation. Only the patient sample was previously reported in other collaborative studies (Cichon *et al*, 2011; Hammer *et al*, 2012; Vassos *et al*, 2012). The controls were genotyped on Illumina OMNI-Express chips at the Life & Brain Center in Bonn, and the patients were also genotyped on Illumina chips (partly on Omni1-Quad).

### **Sweden I sample**

The Sweden I sample consisted of 836 cases and 2,093 controls collected from the following cohorts. St. Göran Bipolar (SBP) cases were recruited from St. Göran's Hospital in Stockholm, Sweden. All participants provided written informed consent to participate in a genetic study of BPD, and the study was approved by the Regional Ethics Committee of Stockholm. Diagnoses were based on physician administered ADE (Spitzer *et al*, 1992) and MINI (Sheehan *et al*, 1998).

Bipol äR cases were identified from the Swedish Bipolar Quality Assurance Registry (Bipol äR). Patient information within the registry includes disease sub-classification, psychosis, age at onset, number of manic and depressive episodes, number of hospitalizations and family history. Participants provided written informed consent to participate in a genetic study of psychiatric disease, and the study was approved by the Regional Ethics Committee of Stockholm.

Hospital Discharge Registry (HDR) bipolar cases were identified from the Swedish Hospital Discharge Registry if they a) have at least two admissions with discharge diagnoses of BPD and b) were born in Sweden or another Nordic country. The register contains a nearly complete record of all individuals hospitalized in Sweden since 1973. Diagnoses were established by an attending physician and were shown to have high sensitivity and specificity (Sellgren *et al*, 2011). The study was approved by the Regional Ethics Committee of Stockholm. All participants provided written informed consent to participate in genetic studies of psychotic disorders and were interviewed by a research nurse about other medical conditions.

The Swedish Bipolar Study Group (SBSG) cases were recruited from the Stockholm County catchment area. All patients provided written informed consent to participate in a genetic study of BPD, and the study was approved by the Regional

Ethics Committee of Stockholm. Diagnoses were made according to the DSM-IV criteria.

Sweden control samples were obtained from the Swedish Hospital Discharge Registry on the condition they had never received discharge diagnoses of BPD, schizophrenia and/or schizoaffective disorder.

### **Sweden II sample**

This sample consisted of 1,415 patients with BPD (62.5% female, age  $\pm$ SD = 53  $\pm$  14, BPD type I =578, BPD type II= 517, NOS=281, SAB = 39, unknown subtype = 4), and 1,271 healthy controls (50.3% female, age  $\pm$ SD= 59  $\pm$  11 years). All subjects were unrelated to each other and ethnically Swedish. Patients with BPD were collected from the Swedish National Quality Assurance Registry for bipolar disorder (Bipol äR), to which all patients with a DSM-IV diagnosis of bipolar I, II, NOS, or schizoaffective disorder are considered for registration at the participating clinics (Sellgren *et al*, 2011). There were no other inclusion or exclusion criteria. Diagnoses were made by the treating physician with longitudinal access to all available clinical information. Controls were also identified from national population registers, and had never received a discharge diagnosis of SCZ or bipolar disorder. Controls were contacted directly in a similar procedure as the cases, gave written informed consent, were interviewed about other medical conditions and visited their family doctor or local hospital laboratory for blood donation. Patients and controls were genotyped on the Illumina Omni Express array, and the genomic inflation factor ( $\lambda$ ) is 1.03.

### **France sample**

The France sample included 451 BPD patients and 1,631 healthy controls. Both BPD and controls were recruited as part of a large study on genetics of BPD in France (Paris-Creteil, Bordeaux, Nancy) with a protocol approved by relevant IRBs and with written informed consent. Patients with BPD were in remission at the time of their inclusion, and were all of French descent dated back to three generations. All patients were assessed by a trained psychiatrist or psychologist using the DIGS (Nurnberger *et al*, 1994) and FIGS. Diagnoses were based on structured interviews supplemented by medical case notes, mood scales and a self-rating questionnaire assessing dimensions. Genotyping of controls were provided by the Centre National de G énotypage (M Lathrop, Evry). Patients and controls were genotyped on the Illumina platform (HumanHap300, HumanHap550, HumanHap 610-quad).

### **Germany II and III sample**

Cases for Germany II and III samples were ascertained from consecutive admissions to the psychiatric inpatient units at the University Hospital W ürzburg and at the Central Institute for Mental Health in Mannheim, University of Heidelberg, as well as at other collaborating psychiatric university hospitals in Germany. DSM-IV lifetime diagnoses of BPD were assigned using a consensus best-estimate procedure, based on all available information, including structured interviews (SCID-I, SADS-L; Germany III) or semi-structured interviews (AMDP; Germany II), medical records, and the family history method. In addition, the OPCRIT system was used for the detailed polydiagnostic documentation of symptoms (McGuffin *et al*, 1991).

Controls for Germany II were ascertained from the population-based Heinz Nixdorf Recall Study (Schmermund *et al*, 2002). Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions.

The controls for Germany III were recruited at the Max Planck Institute of Psychiatry in Munich, Germany, and were selected randomly from a Munich-based community sample. They were collected in the course of genetic studies of major depression, and were therefore screened for the presence of anxiety and affective disorders using the Composite International Diagnostic Screener (WHO-CIDI). Only individuals negative for the above-named disorders were included in the sample. All included controls were Caucasian, 93.04% were of German origin. These subjects thus represent a group of healthy individuals with regard to depression and anxiety. The study was approved by the ethics committee of the Ludwig Maximilians University in Munich, Germany.

All subjects provided written informed consent and were genotyped using the Illumina platform.

### *Australia sample*

The Australia sample included 330 BPD patients and 1,811 healthy controls. Subjects were ascertained through two studies: 1) a BPD pedigree sample (described in McAuley et al. (McAuley *et al*, 2009)) and 2) a specialized Sydney Black Dog Institute BPD clinic sample (described in Mitchell et al. 2009) (Mitchell *et al*, 2009). All subjects were interviewed by trained research staff using the DIGS or SCID, using best-estimate DSM-IV diagnoses derived from those instruments, medical records and FIGS. First, for the pedigree sample, only one BPD subject per family was included in the case sample. Pedigrees were only included in the original genetic study if there was unilineal inheritance, and at least two BPD subjects including at least one with bipolar I disorder. Subjects were ascertained through clinical presentations to the Mood Disorders Unit at the Prince of Wales Hospital in Sydney, direct referrals from Australian clinicians, and BPD consumer organizations. Second, for the clinic sample, subjects comprised consecutive subjects referred by psychiatrists or general practitioners for specialized clinical review. All patients provided written informed consent to participate in this study and the study was approved by the local ethics committee. Patients were included in the MoodDS study and genotyped at the Life & Brain Center in Bonn using the Illumina platform.

Australia controls were drawn from families participating in the Brisbane Longitudinal Twin Study, an unselected community sample recruited to take part in studies of melanoma risk factors, cognition, and other phenotypes. Subjects were not screened for any phenotype relevant to BPD. The study was approved by the ethic committee and all proband gave written informed consent. All subjects were genotyped as a single project by deCODE using the Illumina platform and have been through an extensive QC process including exclusion for non-European ancestry. The sample is overwhelmingly of northern European origin, predominately from the British Isles.

### **Analyses of temporal-spatial expression pattern of CHDH in human brain**

To determine the temporal-spatial expression of CHDH in the human brain, we extracted expression data of CHDH from Human Brain Transcriptome (HBT) (Kang *et al*, 2011) and BrainCloud (Colantuoni *et al*, 2011) databases. The HBT database includes transcriptome of 16 regions comprising the cerebellar cortex, mediodorsal nucleus of the thalamus, striatum, amygdala, hippocampus, and 11 areas of the neocortex. In total, 1,340 tissue samples were collected from 57 developing and adult post-mortem brains. The Brain Cloud database (<http://braincloud.jhmi.edu/>) contains genome-wide gene expression data from the human postmortem dorsolateral prefrontal cortex (DLPFC) of normal subjects (N=261) across the lifespan. More detailed information can be found in the original publications (Colantuoni *et al*, 2011; Kang *et al*, 2011).

**Table S1. Description of individual samples included in this study**

| Sample             | Cases | Case diagnosis        | Diagnosis         | Interview                     | Controls | Genotyping     | $\lambda$ |
|--------------------|-------|-----------------------|-------------------|-------------------------------|----------|----------------|-----------|
| <b>Discovery</b>   |       |                       |                   |                               |          |                |           |
| PGC1               | 7,481 | BPD1,BPD2,SAB,BPD-NOS | DSMIIR,DSM-IV,RDC | multiple                      | 9,250    | multiple       | 1.15      |
| <b>Replication</b> |       |                       |                   |                               |          |                |           |
| Romania            | 380   | BPD1                  | DSM-IV            | SCID-I-P/DIGS                 | 223      | Illumina       | /         |
| Sweden I           | 836   | BPD1,BPD2,BPD-NOS     | DSM-IV            | ADE,MINI                      | 2,093    | Affymetrix 6.0 | 1.07      |
| Sweden II          | 1,415 | BPD1,BPD2,SAB,BPD-NOS | DSM-IV            | /                             | 1,271    | Affymetrix 6.0 | 1.03      |
| France             | 451   | BPD1,BPD2,BPD-NOS     | DSM-IV            | DIGS                          | 1,631    | Illumina       | 1.03      |
| Germany II         | 181   | BPD1,BPD2             | DSM-IV            | AMDP                          | 527      | Illumina       | 1.05      |
| Germany III        | 490   | BPD1,BPD2, BPD-NOS    | DSM-IV            | AMDP, CID-S,<br>SCID-I,SADS-L | 880      | Illumina       | 1.00      |
| Australia          | 330   | BPD1,BPD2,SAB,BPD-NOS | DSM-IV            | SCID,DIGS                     | 1,811    | Illumina       | 1.00      |

**Abbreviations:**

BPD1, bipolar disorder type 1; BPD2, bipolar disorder type 2; BPD-NOS, bipolar disorder not otherwise specified; SAB, schizoaffective disorder (bipolar type);  $\lambda$  = genomic control lambda.

**Table S2. Association of *CHDH* SNPs with BPD in the PGC discovery sample**

| SNP              | Position        | Allele 1 | Allele 2 | Frequency     | P-value         | OR            | SE            |
|------------------|-----------------|----------|----------|---------------|-----------------|---------------|---------------|
| rs3774605        | 53805807        | A        | G        | 0.3607        | 1.88E-05        | 0.8962        | 0.0256        |
| rs3774608        | 53807752        | A        | G        | 0.4016        | 3.84E-06        | 0.8894        | 0.0254        |
| rs3774609        | 53807943        | G        | T        | 0.418         | 2.56E-06        | 0.8878        | 0.0253        |
| rs3796349        | 53808549        | A        | G        | 0.9344        | 0.9406          | 1.0041        | 0.0552        |
| rs2359133        | 53811782        | C        | G        | 0.6393        | 0.000852        | 1.0849        | 0.0244        |
| rs2359132        | 53811977        | A        | G        | 0.9426        | 0.9623          | 0.9974        | 0.0546        |
| rs870280         | 53812286        | C        | T        | 0.0492        | 0.6143          | 1.0293        | 0.0574        |
| rs4687586        | 53813011        | C        | G        | 0.6803        | 0.000642        | 1.0902        | 0.0253        |
| rs6766988        | 53814510        | A        | T        | 0.0984        | 0.4011          | 0.9661        | 0.0411        |
| rs3774614        | 53816504        | C        | T        | 0.4508        | 0.000598        | 0.9216        | 0.0238        |
| rs877484         | 53821964        | A        | G        | 0.4262        | 0.000802        | 0.924         | 0.0236        |
| rs893363         | 53822102        | A        | G        | 0.6148        | 0.000629        | 1.0883        | 0.0247        |
| rs14165          | 53822448        | A        | G        | 0.3115        | 0.000873        | 0.9195        | 0.0252        |
| rs881883         | 53822845        | A        | G        | 0.8852        | 0.8163          | 0.9906        | 0.0406        |
| rs4687587        | 53824550        | A        | G        | 0.3115        | 0.002653        | 0.927         | 0.0252        |
| rs11130381       | 53825045        | C        | T        | 0.4426        | 0.005213        | 0.9361        | 0.0236        |
| rs4687744        | 53825279        | C        | G        | 0.9508        | 0.5753          | 0.9684        | 0.0574        |
| rs4563403        | 53825854        | C        | T        | 0.8852        | 0.9769          | 0.9989        | 0.0392        |
| rs2289209        | 53827875        | C        | T        | 0.9672        | 0.7222          | 0.98          | 0.0569        |
| rs7625247        | 53829108        | G        | T        | 0.582         | 0.008704        | 1.0645        | 0.0238        |
| <b>rs9836592</b> | <b>53830123</b> | <b>C</b> | <b>T</b> | <b>0.3443</b> | <b>0.002321</b> | <b>0.9258</b> | <b>0.0253</b> |
| rs6445606        | 53831090        | C        | T        | 0.3361        | 0.001928        | 0.9238        | 0.0256        |
| rs2241807        | 53832198        | C        | T        | 0.4426        | 0.008085        | 0.9392        | 0.0237        |
| rs9001           | 53832957        | G        | T        | 0.082         | 0.4201          | 1.0389        | 0.0473        |
| rs2276838        | 53833204        | C        | T        | 0.4426        | 0.00836         | 0.9394        | 0.0237        |
| rs7626693        | 53833581        | C        | T        | 0.459         | 0.01367         | 0.9431        | 0.0238        |
| rs9835128        | 53835143        | A        | C        | 0.1066        | 0.1008          | 1.0661        | 0.039         |
| rs13317328       | 53845880        | A        | C        | 0.877         | 0.1877          | 0.9363        | 0.05          |
| rs11718497       | 53847057        | C        | G        | 0.377         | 0.2054          | 0.9695        | 0.0244        |
| rs920253         | 53847793        | G        | T        | 0.9918        | 0.6157          | 1.0711        | 0.1369        |
| rs930367         | 53848618        | C        | T        | 0.0492        | 0.1372          | 1.1122        | 0.0716        |
| rs6801605        | 53851258        | A        | G        | 0.3443        | 0.3331          | 0.9771        | 0.0239        |
| rs6445607        | 53852189        | G        | T        | 0.3689        | 0.3568          | 0.9782        | 0.024         |
| rs6445608        | 53852273        | C        | G        | 0.6311        | 0.3377          | 1.0233        | 0.0241        |
| rs3774616        | 53852973        | C        | T        | 0.0574        | 0.04885         | 1.1599        | 0.0753        |
| rs2289207        | 53853424        | C        | T        | 0.9672        | 0.3             | 1.1219        | 0.111         |
| rs17641133       | 53853637        | A        | T        | 0.2541        | 0.1088          | 0.9581        | 0.0267        |
| rs2289205        | 53853656        | C        | T        | 0.7377        | 0.1206          | 1.045         | 0.0283        |
| rs7627178        | 53856511        | A        | G        | 0.6639        | 0.2527          | 1.0296        | 0.0255        |
| rs1025690        | 53857703        | A        | G        | 0.6885        | 0.07896         | 1.0471        | 0.0262        |
| rs2276839        | 53857943        | C        | G        | 0.2623        | 0.1063          | 0.9575        | 0.0269        |
| rs1025689        | 53858762        | C        | G        | 0.3279        | 0.3215          | 0.9749        | 0.0257        |
| rs4687751        | 53858950        | C        | T        | 0.3443        | 0.3144          | 0.9745        | 0.0257        |
| rs9878562        | 53864028        | C        | T        | 0.5246        | 0.8418          | 1.0046        | 0.0231        |
| rs999514         | 53864889        | C        | T        | 0.4344        | 0.8612          | 0.9958        | 0.0239        |
| rs999515         | 53865021        | C        | T        | 0.3607        | 0.9145          | 1.0027        | 0.0248        |
| rs2276840        | 53866137        | C        | G        | 0.6066        | 0.8288          | 1.0053        | 0.0244        |
| rs2276841        | 53866163        | A        | G        | 0.8852        | 0.8539          | 0.993         | 0.0379        |
| rs9840079        | 53867681        | G        | T        | 0.4918        | 0.893           | 0.9969        | 0.0231        |
| rs2232345        | 53867760        | A        | T        | 0.0492        | 0.5048          | 0.9505        | 0.0761        |
| rs3821869        | 53868880        | A        | C        | 0.377         | 0.846           | 0.9953        | 0.0244        |
| rs6766099        | 53869452        | C        | T        | 0.9016        | 0.9892          | 0.9995        | 0.0381        |

**Table S3. Genes differentially expressed between BPD patients and healthy controls**

| Genes                 | RNA-seq analyses                      |                                      | Microarray analyses                   |   |
|-----------------------|---------------------------------------|--------------------------------------|---------------------------------------|---|
|                       | Akula <i>et al.</i> (2014)<br>P-value | Zhao <i>et al.</i> (2015)<br>P-value | Akula <i>et al.</i> (2014)<br>P-value | Seifuddin <i>et al.</i> (2013)<br>P-value |
| <b>Up-regulated</b>   |                                       |                                      |                                       |   |
| <i>ALDH4A1</i>        | 0.000124                              | 0.00615                              | 0.0470                                | n.s.                                      |
| <i>PBXIP1</i>         | 0.000824                              | 0.00267                              | n.s.                                  | 0.0526                                    |
| <i>GALM</i>           | 0.00736                               | 0.00868                              | n.s.                                  | n.s.                                      |
| <b><i>CHDH</i></b>    | <b>0.00811</b>                        | <b>0.00251</b>                       | <b>0.00497</b>                        | <b>0.0361</b>                             |
| <i>TP53BP2</i>        | 0.00855                               | 0.00452                              | n.s.                                  | 0.00171                                   |
|                       |                                       |                                      |                                       |   |
| <b>Down-regulated</b> |                                       |                                      |                                       |   |
| <i>VIP</i>            | 0.00421                               | 0.00124                              | 0.00625                               | n.s.                                      |
| <i>HIVEP2</i>         | 0.00646                               | 0.00175                              | n.s.                                  | 0.00997                                   |
| <i>FAM49A</i>         | 0.00905                               | 0.00363                              | 0.0281                                | n.s.                                      |

**Table S4. Association of rs9836592 [T] with BPD in different European samples**

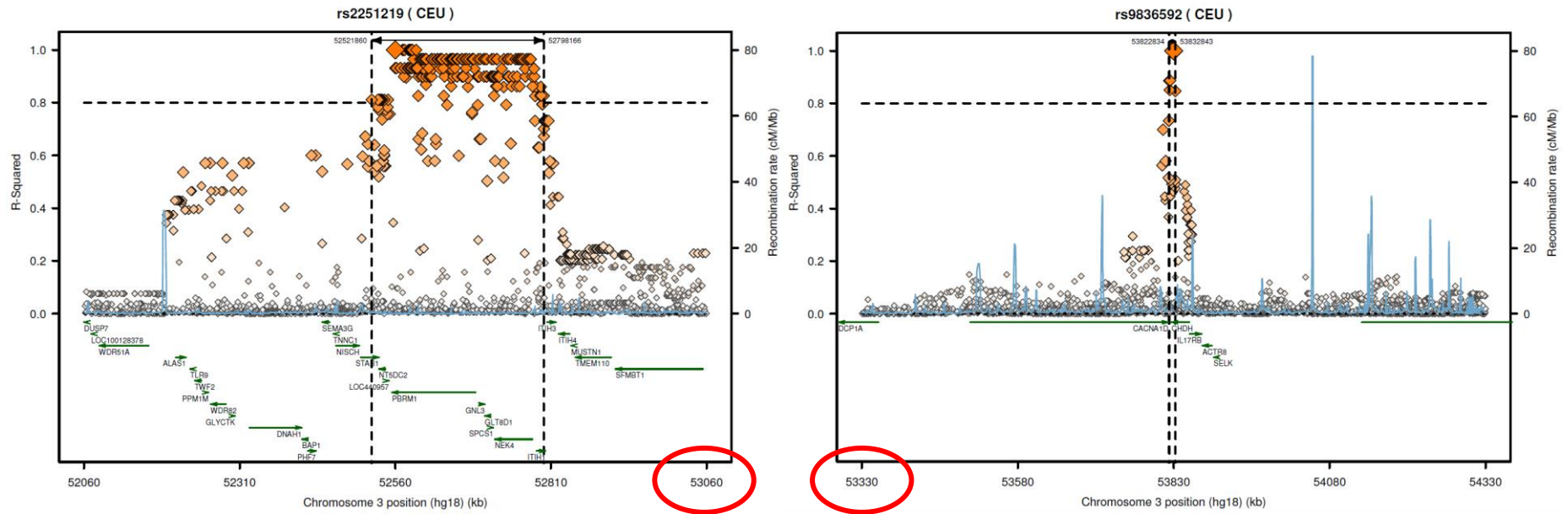
| <b>Sample</b> | <b>N_Case</b> | <b>N_Control</b> | <b>P-value</b> | <b>OR</b> | <b>95%CI</b>   |
|---------------|---------------|------------------|----------------|-----------|----------------|
| Discovery     | 7,481         | 9,250            | 0.00232        | 1.080     | [1.028; 1.135] |
| Romania       | 380           | 223              | 0.0555         | 1.217     | [0.956; 1.551] |
| Sweden I      | 836           | 2,093            | 0.498          | 1.000     | [0.884; 1.131] |
| Sweden II     | 1,415         | 1,271            | 0.137          | 1.073     | [0.946; 1.218] |
| France        | 451           | 1,631            | 0.248          | 1.064     | [0.890; 1.271] |
| Germany II    | 181           | 527              | 0.0836         | 1.209     | [0.924; 1.583] |
| Germany III   | 490           | 880              | 0.0757         | 1.128     | [0.957; 1.330] |
| Australia     | 330           | 1,811            | 0.169          | 0.917     | [0.768; 1.095] |



**Table S5. Association of rs9836592 with *CHDH*'s nearby gene expression in several tissues. P-value is shown in the table.**

|                              | <b>CACNA1D</b> | <b>IL17RB</b>         | <b>ACTR8</b> | <b>SELK</b> |
|------------------------------|----------------|-----------------------|--------------|-------------|
| <b>Cerebellum</b>            | 0.64           | 0.12                  | 0.81         | 0.85        |
| <b>Cerebellar Hemisphere</b> | 0.77           | 0.10                  | 0.036        | 0.55        |
| <b>Putamen</b>               | 0.096          | 0.34                  | 0.00038      | 0.35        |
| <b>Nerve Tibial</b>          | 0.53           | $9.8 \times 10^{-15}$ | 0.59         | 0.085       |
| <b>Hypothalamus</b>          | 0.58           | 0.0078                | 0.0020       | 0.45        |
| <b>Hippocampus</b>           | 0.82           | 0.70                  | 0.13         | 0.16        |
| <b>Muscle Skeletal</b>       | 0.063          | 0.44                  | 0.057        | 0.30        |
| <b>Thyroid</b>               | 0.86           | 0.00061               | 0.015        | 0.96        |
| <b>Testis</b>                | 0.20           | 0.79                  | 0.013        | 0.10        |

Figure S1. The locations and LD patterns of rs2251219 and rs9836592 in European populations.



**Figure S2. Association of rs9836592 with the expression of genes in BrainCloud** (Colantuoni *et al.*, 2011).

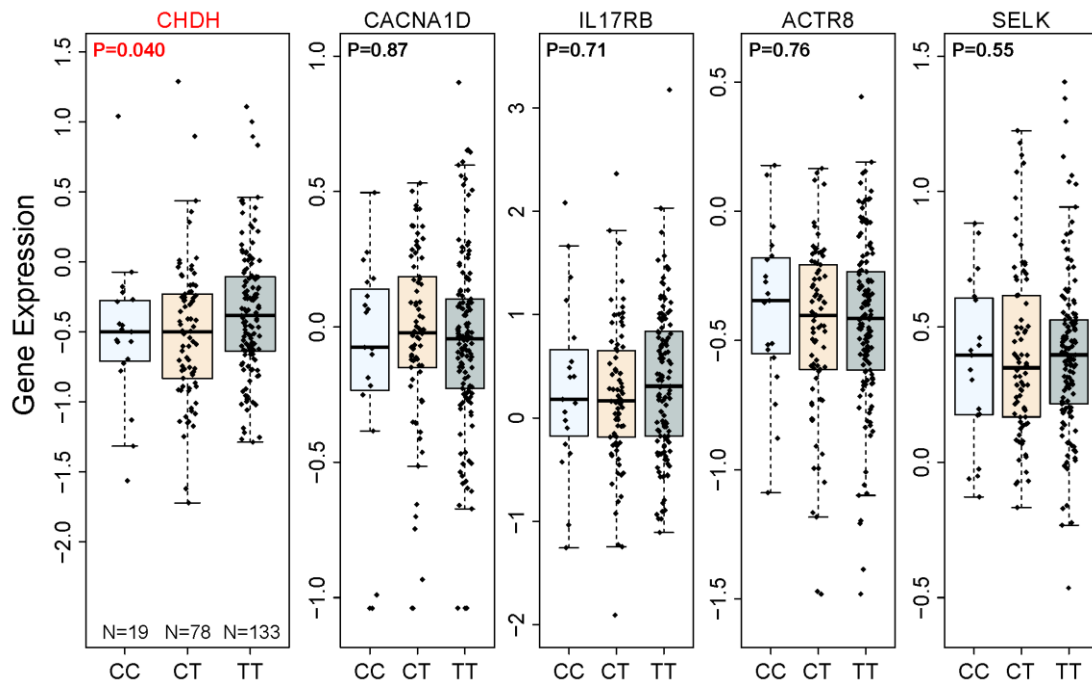
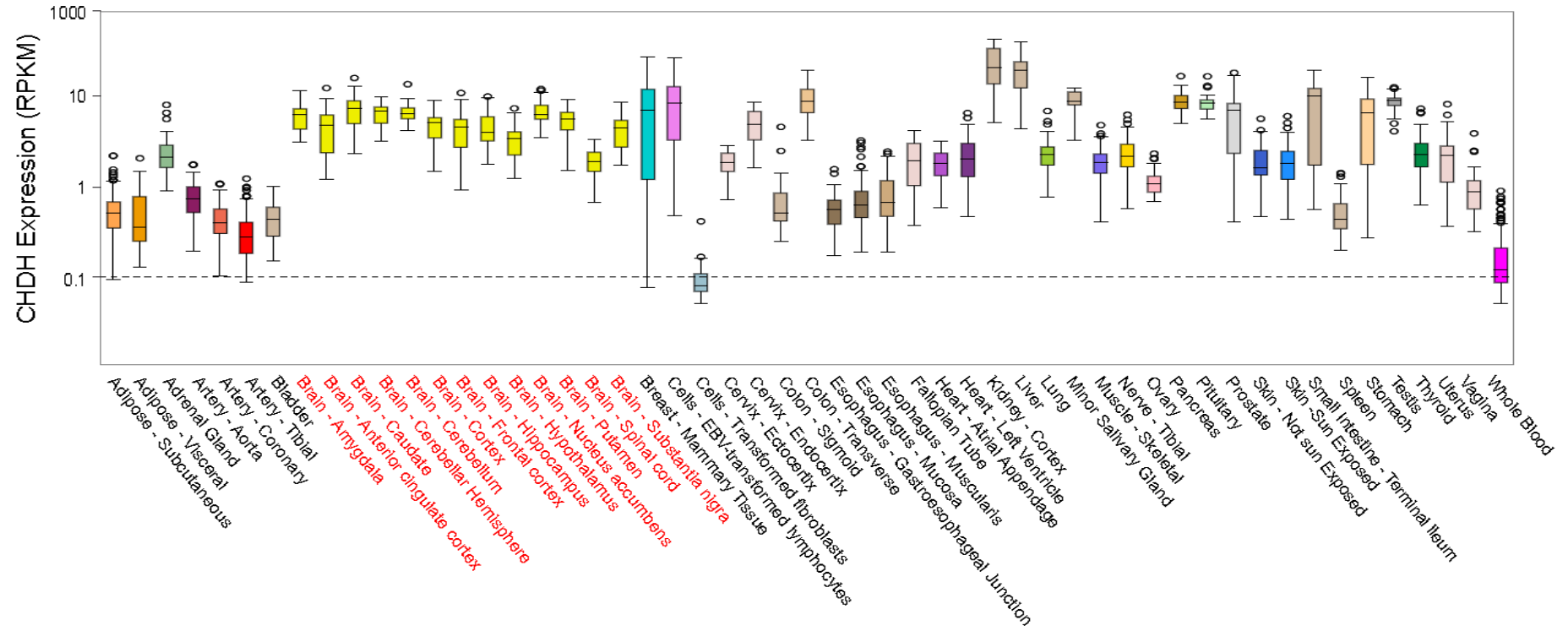
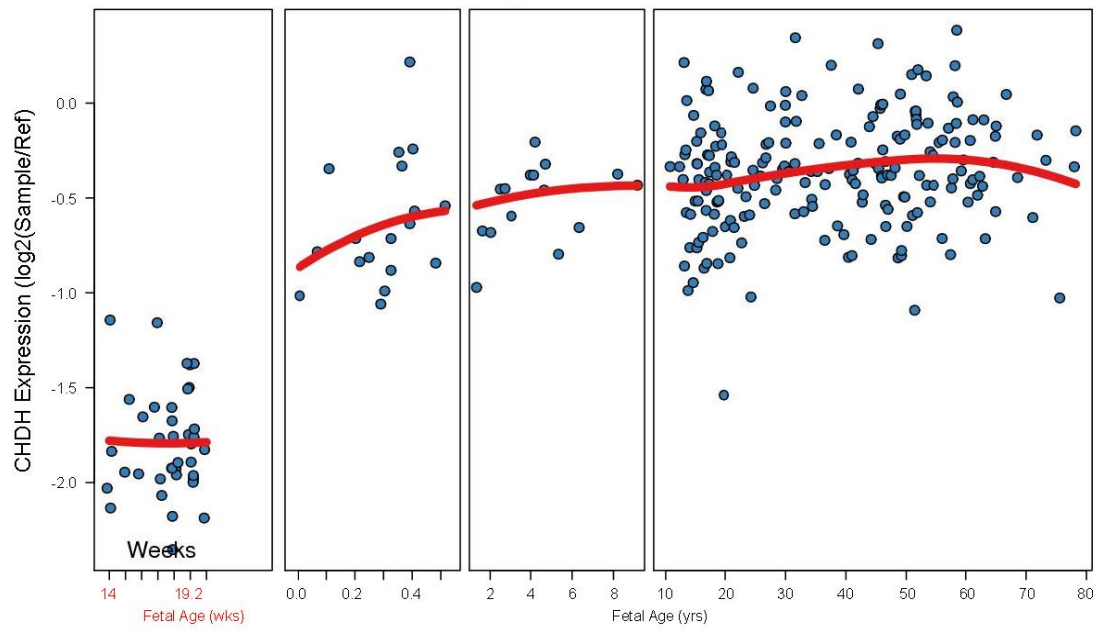


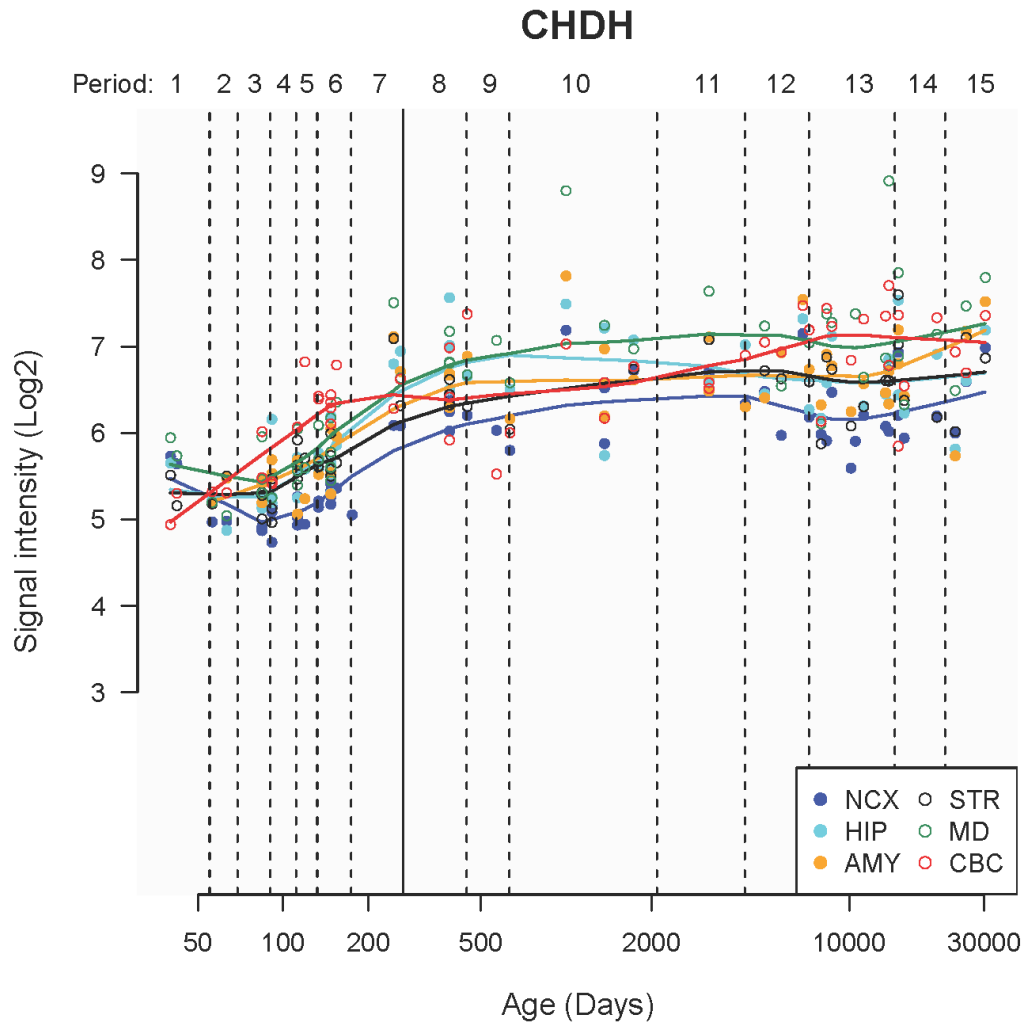
Figure S3. Spatial expression profiling of *CHDH* in human brain tissues from GTEx (GTEx Consortium, 2013).



**Figure S4. Temporal expression profiling of *CHDH* in human brain DLPFC from BrainCloud (Colantuoni *et al*, 2011).**



**Figure S5. Temporal expression pattern of *CHDH* in different human brain regions in Human Brain Transcriptome (Kang *et al.*, 2011).**



Notes: AMY, amygdala; CBC, cerebellar cortex; HIP, hippocampus; MD, mediodorsal nucleus of the thalamus; NCX, neocortex; STR, striatum.

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