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).

BipolärR cases were identified from the Swedish Bipolar Quality Assurance Registry (BipolärR). 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 ± SD = 53 ± 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 ± SD= 59 ± 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 (Bipolär), 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 Génotypage (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 Würzburg 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 MooDS 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 HTB 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	λ
Discovery							
PGC1	7,481	BPD1,BPD2,SAB,BPD-NOS	DSMIIR,DSM-IV,RDC	multiple	9,250	multiple	1.15
Replication							
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, 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); λ = 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
rs9836592	53830123	C	T	0.3443	0.002321	0.9258	0.0253
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

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

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

Sample	N_Case	N_Control	P-value	OR	95%CI
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.

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

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

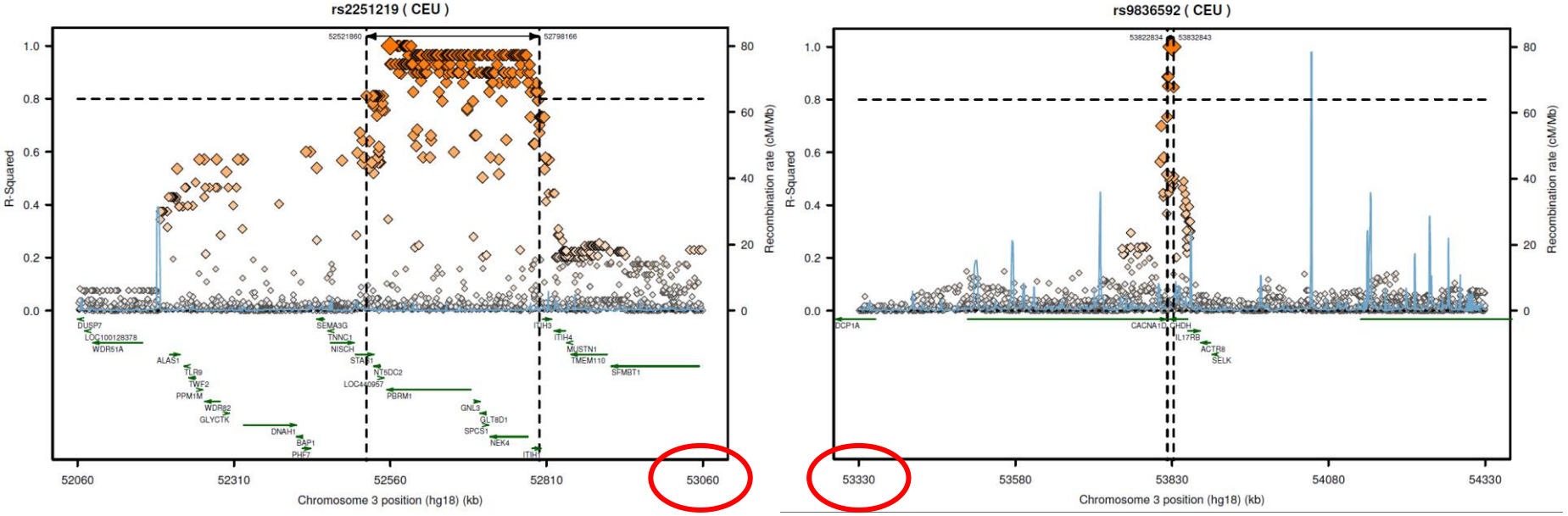


Figure S2. Association of rs9836592 with the expression of genes in BrainCloud (Colantuoni *et al*, 2011)**.**

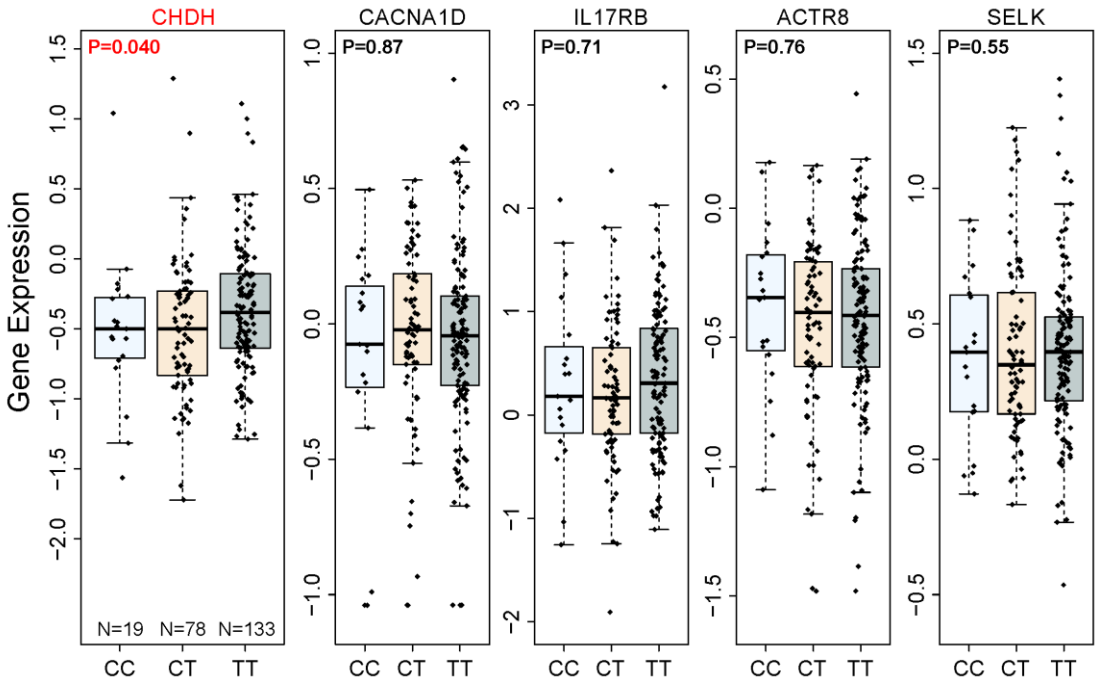


Figure S3. Spatial expression profiling of *CHDH* in human brain tissues from GTEx (GTEx Consortium, 2013)**.**

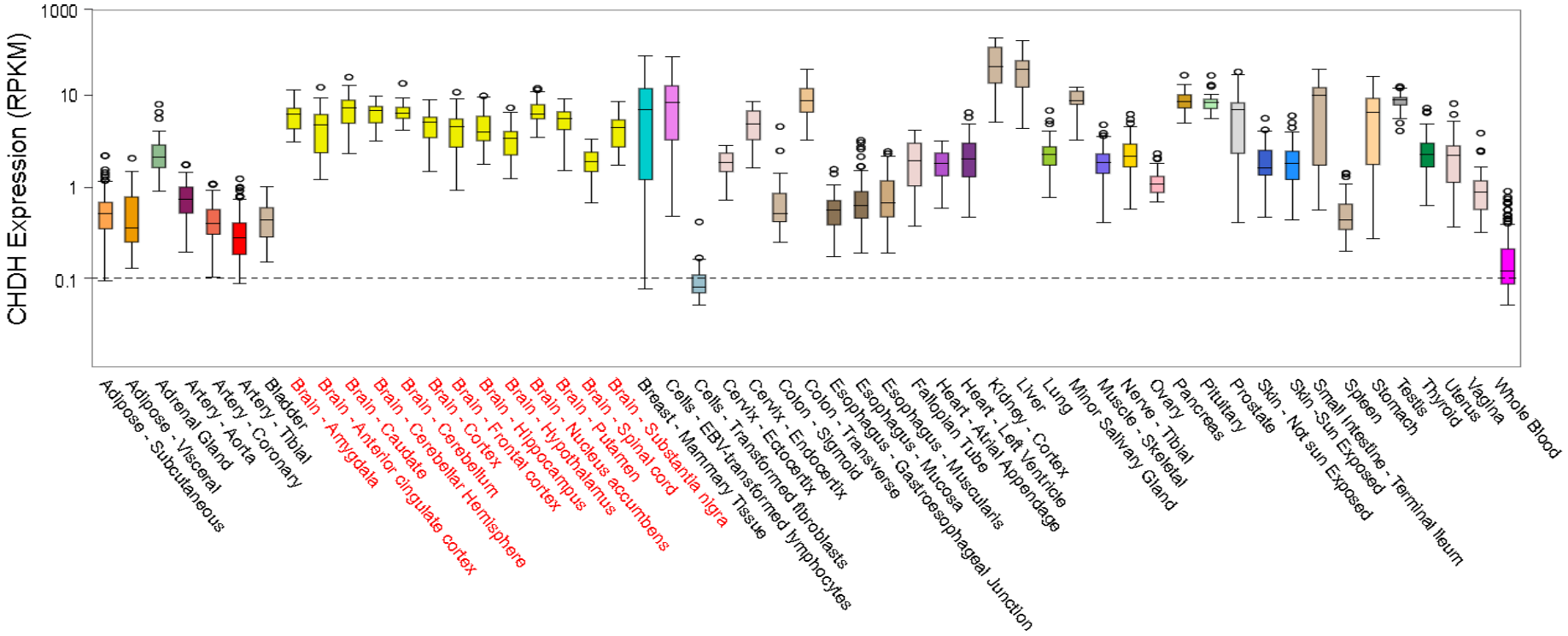


Figure S4. Temporal expression profiling of *CHDH* in human brain DLPFC from BrainCloud (Colantuoni *et al*, 2011)**.**

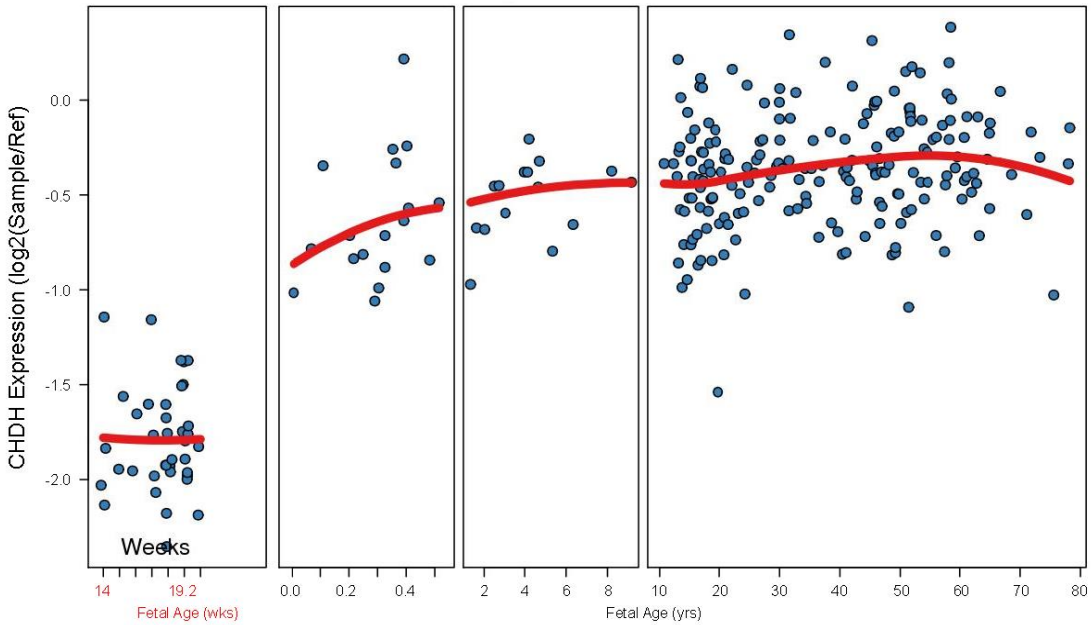
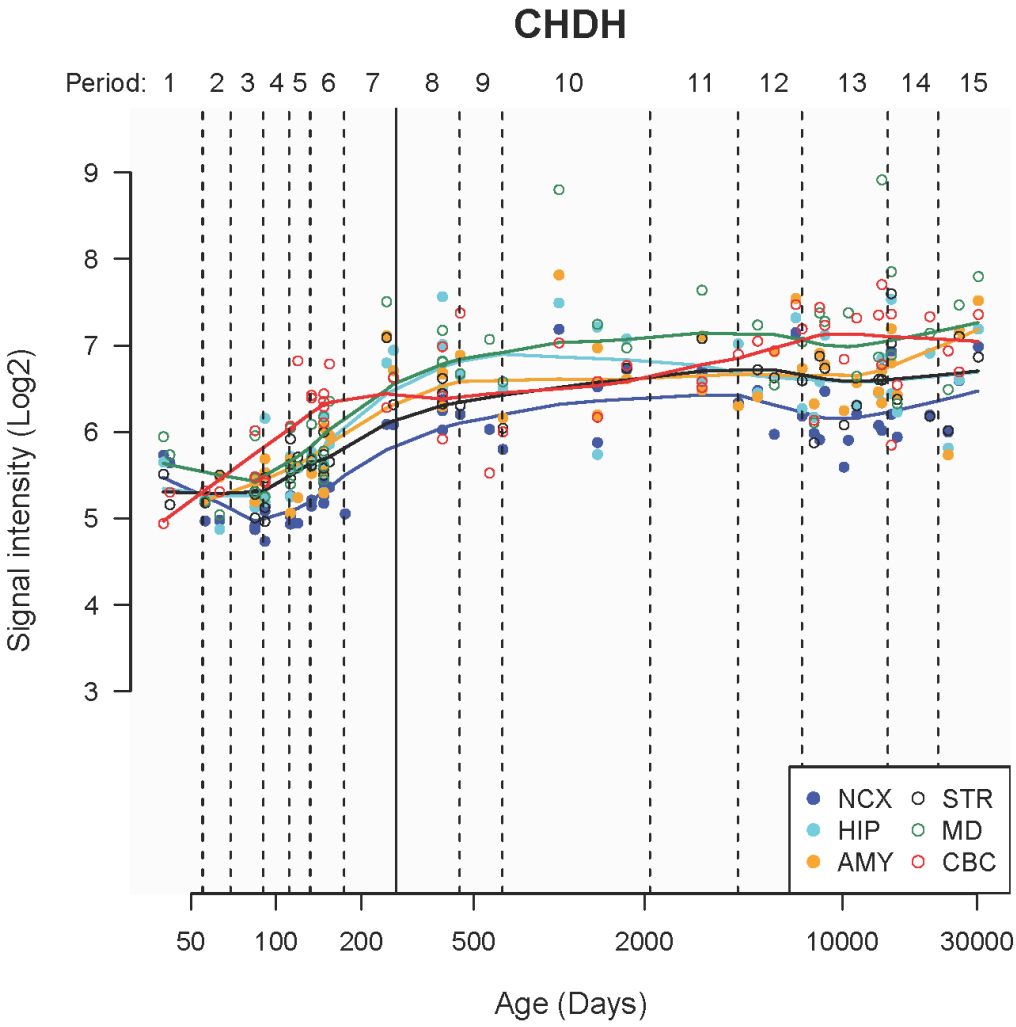


Figure S5. Temporal expression pattern of *CHDH* in different human brain regions in Human Brain Transcriptome (Kang *et al*, 2011)**.**



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

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