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High-resolution chromosome ideogram representation of recognized genes for bipolar disorder

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Abstract

Bipolar disorder (BPD) is genetically heterogeneous with a growing list of BPD associated genes reported in recent years resulting from increased genetic testing using advanced genetic technology, expanded genomic databases, and better awareness of the disorder. We compiled a master list of recognized susceptibility and genes associated with BPD identified from peer-reviewed medical literature sources using PubMed and by searching online databases, such as OMIM. Searched keywords were related to bipolar disorder and genetics. Our compiled list consisted of 290 genes with gene names arranged in alphabetical order in tabular form with source documents and their chromosome location and gene symbols plotted on high-resolution human chromosome ideograms. The identified genes impacted a broad range of biological pathways and processes including cellular signaling pathways particularly cAMP and calcium (e.g., *CACNA1C*, *CAMK2A*, *CAMK2D*, *ADCY1*, *ADCY2*); glutamatergic (e.g., *GRIK1*, *GRM3*, *GRM7*), dopaminergic (e.g., *DRD2*, *DRD4*, *COMT*, *MAOA*) and serotonergic (e.g., *HTR1A*, *HTR2A*, *HTR3B*) neurotransmission; molecular transporters (e.g., SLC39A3, SLC6A3, SLC8A1); and neuronal growth (e.g., *BDNF*, *IGFBP1*, *NRG1*, *NRG3*). The increasing prevalence of BPD calls for better understanding of the genetic etiology of this disorder and associations between the observed BPD phenotype and genes. Visual representation of genes for bipolar disorder becomes a tool enabling clinical and laboratory geneticists, genetic counselors, and other health care providers and researchers easy access to the location and distribution of currently recognized BPD associated genes. Our study may also help inform diagnosis and advance treatment developments for those affected with this disorder and improve genetic counseling for families.

Keywords

Bipolar disorder; Chromosome ideograms; Major affective disorder; Manic-depressive illness; Susceptibility genes

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Conflicts of interest

The authors declare no conflict of interest.

1. Introduction

Bipolar disorder (BPD) or major affective disorder is largely undiagnosed but known to cause unusual shifts in behavior, including mood, activity levels, and ability to perform everyday tasks. According to the Diagnostic and Statistical Manual for Mental Disorders, fifth edition (DSM-5), BPD can be separated into four basic types: Bipolar I Disorder (BP-I), Bipolar II Disorder (BP-II), Bipolar Disorder Not Otherwise Specified (BP-NOS), and Cyclothymic Disorder. The diagnosis is dependent on severity and length of the manic and depressive phases [Hirschfeld et al., 2000, 2003a, 2003b; Juvenile Bipolar Research Foundation (http://www.jbrf.org/diagnosis-by-the-dsm/); National Institute of Mental Health (http://www.nimh.nih.gov/health/topics/bipolar-disorder/index.shtml#part_145403)]. The twelve month prevalence of BPD is 1.5% for the adult population in the U.S., 0.4% for BP-I, 0.3% for BP-II, and 0.8% for BP-NOS. The lifetime prevalence of BPD in the U.S. population is 2.4% for the total population; 0.6% for BP-I, 0.4% for BP-II, and 1.4% for BP-NOS (Merikangas et al., 2011). Men and women are equally affected by BPD, but women are three times more likely than men to experience the rapid cycling process and tend to experience the depressive and mixed episodes more often than men (Merikangas et al., 2011). Most individuals are diagnosed with bipolar disorder around the age of 25 years, but some individuals are diagnosed as young as six years of age or as late as 40 and 50 years [Birmaher et al., 2006; Geller et al., 2004; Depression and Bipolar Support AllianceDepression and Bipolar Support Alliance (http://www.dbsalliance.org/site/PageServer?pagename=education_statistics_bipolar_disorder)]. Given the nature of the disorder, it is common for individuals with BPD to be misdiagnosed as having another mental illness, which can hinder recognition and treatment [Depression and Bipolar Support Alliance (http://www.dbsalliance.org/site/PageServer?pagename=education_statistics_bipolar_disorder)]. BPD often coexists with other Axis I and Axis II disorders [e.g. substance abuse, anxiety disorders (such as agoraphobia, post-traumatic stress disorder, and social phobia), and eating disorders] with reported rates of lifetime psychiatric comorbidity in bipolar I samples ranging from 50% to 70% (McElroy et al., 2001). Approximately 20% of the children and adolescents experiencing major depression will develop bipolar disorder within five years of being diagnosed with depression (Birmaher et al., 2006; McClellan et al., 2007). Almost one-third of adolescents with depression are actually experiencing early onset of bipolar disorder.

Numerous twin and family studies have supported a genetic contribution to the risk of developing BPD. Monozygotic twins show greater concordance with psychopathology than dizygotic twins and individuals with affected relatives show an increased chance of developing bipolar and/or unipolar depression (Smoller and Finn, 2003). One affected parent is associated with a 15 to 25% elevation in risk of BPD while two affected parents shows a 50 to 75% increase [Smoller and Finn, 2003; Depression and Bipolar Support Alliance (http://www.dbsalliance.org/site/PageServer?pagename=education_statistics_bipolar_disorder)]. Never-the-less, bipolar disorder is a complex genetic disorder that does not follow Mendelian inheritance patterns with no identifiable “gene of major effect” found for the majority of BPD cases. There are also several chromosomal regions, susceptibility loci and implicated genes for BPD that have

been repeatedly reported as associated with the disorder through linkage, candidate and genome-wide association studies (Craddock and Jones, 1999; Craddock et al., 2005). Interactions between numerous genes in multiple overlapping pathways and functions reduce the likelihood of one-to-one correspondence for any single "causal" bipolar disorder gene mutation (Potash and DePaulo, 2000).

Over the last few decades, researchers have identified numerous candidate genes associated with BPD using various methodologies, including genotyping single-nucleotide polymorphisms (SNPs), identifying cytogenetic abnormalities (i.e., chromosomal breakpoints which lead to the loss or alteration of specific genes), or convergent functional genomics (Cichon et al., 2009). We used existing literature and genomic databases to obtain evidence to compile a master list of currently recognized genes with their locations plotted on high-resolution chromosome ideograms (850 band level) associated with BPD. In tabular form, we listed the individual gene symbol, expanded name, and chromosome location alongside the reference source providing the information.

2. Material and methods

We used computer-based internet websites and PubMed (https://www.ncbi.nlm.nih.gov/pubmed) to search for key words based on the genetics of bipolar disorder. Articles were obtained by searching PubMed and Online Mendelian Inheritance in Man (OMIM: http://www.ncbi.nlm.nih.gov/omim) databases with the following search words: *bipolar disorder (BPD), bipolar, major affective disorder, bipolar affective disorder (BPAD), bipolar syndrome, and manic depressive psychosis*. We examined literature found in medical journals after our search for genetic involvement for BPD. Some articles we found had their own compilation of susceptibility genes for BPD with references to their own sources which we then further studied (Thomson et al., 2005; Le-Niculescu et al., 2009; Cichon et al., 2009; Shinozaki and Potash, 2014). The articles were then prioritized based on the following considerations: *sample size, use of standardized diagnostic criteria, types of genetic testing such as genome wide association studies and validated methods (e.g., convergent functional genomics, genotyping SNPs or identifying cytogenetic abnormalities), and quality with reliability of the genetic data and presentation*. GeneCards (http://www.genecards.org/) was the primary source for determining the location of the gene or gene locus. The cytogenetic location of the gene was provided by Ensembl, Entrez Gene, or the Human Genome Organization Gene Nomenclature Committee (HGNC).

BPD is a heterogeneous disorder involving many genes acting individually or in combination and responsive to environmental stimuli. We compiled a list of genes from the major sources and their references for a total of 290 genes. Our paper focused on genes associated with BPD by at least one mechanism of proven association with or susceptibility to BPD. Research articles were not limited to causal relationships to BPD. For example, Le-Niculescu and others used convergence of microsatellite markers for which at least one published study showed evidence for linkage for BPD, or a positive association study for the gene itself reported in previous literature (Le-Niculescu et al., 2009). Many of the genes on our list were found in multiple research studies and were reported more than once for being associated with BPD. Some studies considered target neurochemical pathways rather than

susceptibility loci. These genes were included on our list if they were also recognized by a peer-reviewed publication (e.g., PubMed) with supporting evidence (e.g., GWAS, informative SNPs, genetic linkage, or identified gene mutations) as a BPD associated gene (Le-Niculescu et al., 2009; Cichon et al., 2011). Other supporting genetic evidence can be found in the National Center for Biotechnology Resources at https://www.ncbi.nlm.nih.gov/gene.

3. Results

By using online databases and existing literature in peer-reviewed journals, we were able to compile a master list of 290 recognized genes associated with BPD. These genes were clinically relevant, or related to susceptibility of BPD. The position for each of the recognized or susceptibility genes for BPD were plotted on the high-resolution chromosome ideograms (850 band level), as shown in Fig. 1. We have also included gene symbols, expanded names, chromosome band location and reference sources in Table 1 for the 290 genes recognized as playing a role in BPD. The distribution of BPD genes is shown in Table 2 among individual chromosomes and chromosome arms arranged by the size for each chromosome (largest chromosome represented by the smallest number) in relationship to the proportion of total genes for BPD.

The majority of the genes listed in Table 1 are located on chromosomes 1, 2, 3, 4, 5 6, 7, 8, 9, 10, 11, 13, 16, 18, and 22 in accordance with previous reports examining polymorphisms and chromosomal breakpoints of known and candidate genes for BPD (Potash and DePaulo, 2000; Etain et al., 2012). One of the smallest chromosomes (i.e., 22) contained more BPD genes in relationship to its size (i.e., 4.1%) than other comparable chromosomes. The X chromosome which accounts for about 5.6% of the genome contained only 1.0% of the BPD genes. The genes identified in our investigation impacted a broad range of biological pathways and processes including cellular signaling pathways for cAMP and calcium (e.g., *CACNA1C*, *CAMK2A*, *CAMK2D*, *ADCY1*, *ADCY2*); glutamatergic (e.g., *GRIK1*, *GRM3*, *GRM7*), dopaminergic (e.g., *DRD2*, *DRD4*, *COMT*, *MAOA*) and serotonergic (*e.g.*, *HTR1A*, *HTR2A*, *HTR3B*) neurotransmission; molecular transporters (*e.g.*, *SLC39A3*, *SLC6A3*, *SLC8A1*); and neuronal growth (e.g., *BDNF*, *IGFBP1*, *NRG1*, *NRG3*). These gene classes influence neurotransmission and psychological functioning through direct and indirect effects on neuronal activity, growth, development, maintenance and remodeling. These genes overlap with biological markers and genetic factors associated with other psychiatric disorders such as schizophrenia, (e.g., *BDNF*, *CACNA1*, *DISC1*), major depressive and anxiety disorders (e.g., *TPH2*, *HTR2A*) involving developmental processes (e.g., *NRG1*, *NRG3*).

4. Discussion

The advent of genetic testing to identify the predisposition for BPD has increased understanding of the genetic etiology of BPD and the application of genetic testing should facilitate research and treatment development. We illustrated a master list of susceptibility genes and genes that are associated with BPD in our results by plotting the individual genes on high-resolution chromosome ideograms and generated a tabular form with references in

order to inform more individuals about the necessity for genetic testing and treatment for BPD.

The transmission of BPD does not appear to manifest through a simple Mendelian inheritance with a single allele (dominant) or two alleles (recessive) pattern instead showing incomplete penetrance, etiological heterogeneity and high prevalence (Kerner, 2015). Similarly, multivariate threshold models conceptualized as an accumulation of traits normally distributed throughout the genome are not strongly supported to achieve some threshold for expression. Rather, BPD appears to be a product of a combination of genetic, neurochemical, and environmental influences. The expression or development of bipolar disorder may be due to epistasis (interaction of multiple genes) or other complex mechanisms such as genomic imprinting or dynamic mutations with environmental contributions (Craddock and Jones, 1999). An intricate oligogenic quasi-Mendelian pattern has been proposed whereby a small number of mutations accumulate in a select biological pathway that is only tied to expression of the phenotype when released by environmental influences (Kerner, 2015). Symptoms of bipolar disorder parallel other genetically influenced psychiatric disorders including schizophrenia, depression and anxiety (Krishnan, 2005) and is, not surprisingly, impacted by overlapping genetic constructs (e.g., *BDNF*, *DISC1*, *HTR2A*, *TPH2*).

Our list of genes for BPD reflects the current status of recognized genes with clinical relevance but susceptibility and new genes are continually being identified. Not all genes in the list are equally significant or certainly causative for all individuals with BPD. Similarly, our results reflect gene-level associations and do not provide evidence of individual SNP- or CNV-level contributions to pathology. The list is particularly suited to the evaluation of structural genomic data (e.g., DNA microarrays) for copy number variations impacting genomic regions and genes of interest which may involve large regions and multiple candidate genes or encompass known genetic syndromes. Phenotype and severity can be predicted to be proportional to the number of candidate genes impacted by the CNV – highlighting the clinical value of spatial representation of the gene list and whether the region is duplicated or deleted. The effect of any individual SNP depends upon both the physiological relevance of the gene to neurodevelopmental processes and the impact of the specific sequence variation or mutation on the expression and function of the gene product (i.e., synonymous vs. non-synonymous). Non-synonymous variations leading to a change of the codon or reading frame (e.g., frameshift mutation, stop codon generation) have greater predicted impact on gene expression and thus stronger ties to pathology. Advances in genomic technology will facilitate the identification and characterization of novel SNPs among the gene candidates and improve understanding of the relative contributions of selected SNP or CNVs to the general disease prevalence.

Combinations of single nucleotide polymorphisms (SNPs) which alter the genetic code, creating a higher likelihood of developing bipolar disorder, are reportedly more common than chromosomal breakpoints at the susceptibility regions for BPD. For example, SNPs within the brain derived neurotrophic factor (*BDNF*) gene, located in the 11p14, region are reported to result in a modification of the processing and trafficking of the *BDNF* gene and increased susceptibility to BPD (Craddock et al., 2005). The *ABCA13* gene was also

identified as a candidate gene for both bipolar and schizophrenia disorders once it was initially discovered by a chromosome abnormality in a schizophrenic patient (Knight et al., 2009). The *ABCA13* gene was then resequenced and multiple rare coding variants identified. These variants were genotyped in bipolar cohorts, which led to the conclusion that 4.0% of the population contained a variant which could contribute to bipolar disorder (Knight et al., 2009). Multiple genome-wide association studies (GWAS) testing for SNPs in independent bipolar cases and controls often generate strong signals for gene associations with bipolar disorder (Sklar et al., 2011). For example, results from the first GWAS for BPD reported in 2007 determined that the strongest signals for an association were found in five genes: *BDNF* at 11p14, *DAOA* at 13q33, *DTNBP1* at 6p22, *DISC1* at 1q42, and *NRG1* at 8p12, and the *SNP* rs420259 at 16p12 (Burton et al., 2007). Since this initial study, additional GWAS reports (e.g., Sklar et al., 2008; Ferreira et al., 2008) and a collection of genetic studies examining bipolar disorder did implicate genes that were consolidated in 2014 by Shinozaki and Potash (Shinozaki and Potash, 2014) with a list of candidate genes summarized from 15 studies (e.g., Baum et al., 2008a, 2008b; Sklar et al., 2011; Ou et al., 2015). These genes overlapped with biological markers and genetic factors associated with other psychiatric disorders such as schizophrenia, (e.g., *BDNF*, *CACNA1*, *DISC1*), major depressive and anxiety disorders (e.g., *TPH2*, *HTR2A*) and involved in developmental processes.

Our list of candidate genes and visual representation of their locations on high-resolution chromosome ideograms for bipolar disorder provide an informative perspective of the pathophysiology of BPD to facilitate research, accurate diagnosis and genetic counseling, treatment development and classification of BPD (Craddock and Jones, 1999). The authors encourage the use of this collection of currently associated recognized susceptibility genes for BPD in the evaluation of patients presenting for genetic services and for a more accurate understanding of the role of genetics in BPD, a genetically heterogeneous disorder.

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Abbreviations:

BPD	bipolar disorder
BP-I	Bipolar I Disorder
BP-II	Bipolar II Disorder
BP-NOS	Bipolar Disorder Not Otherwise Specified
cAMP	cyclic adenosine monophosphate

DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual for Mental Disorders, fifth edition
FDA	Food and Drug Administration
GWAS	genome-wide association studies
OMIM	online Mendelian inheritance in man
SNPs	single nucleotide polymorphisms

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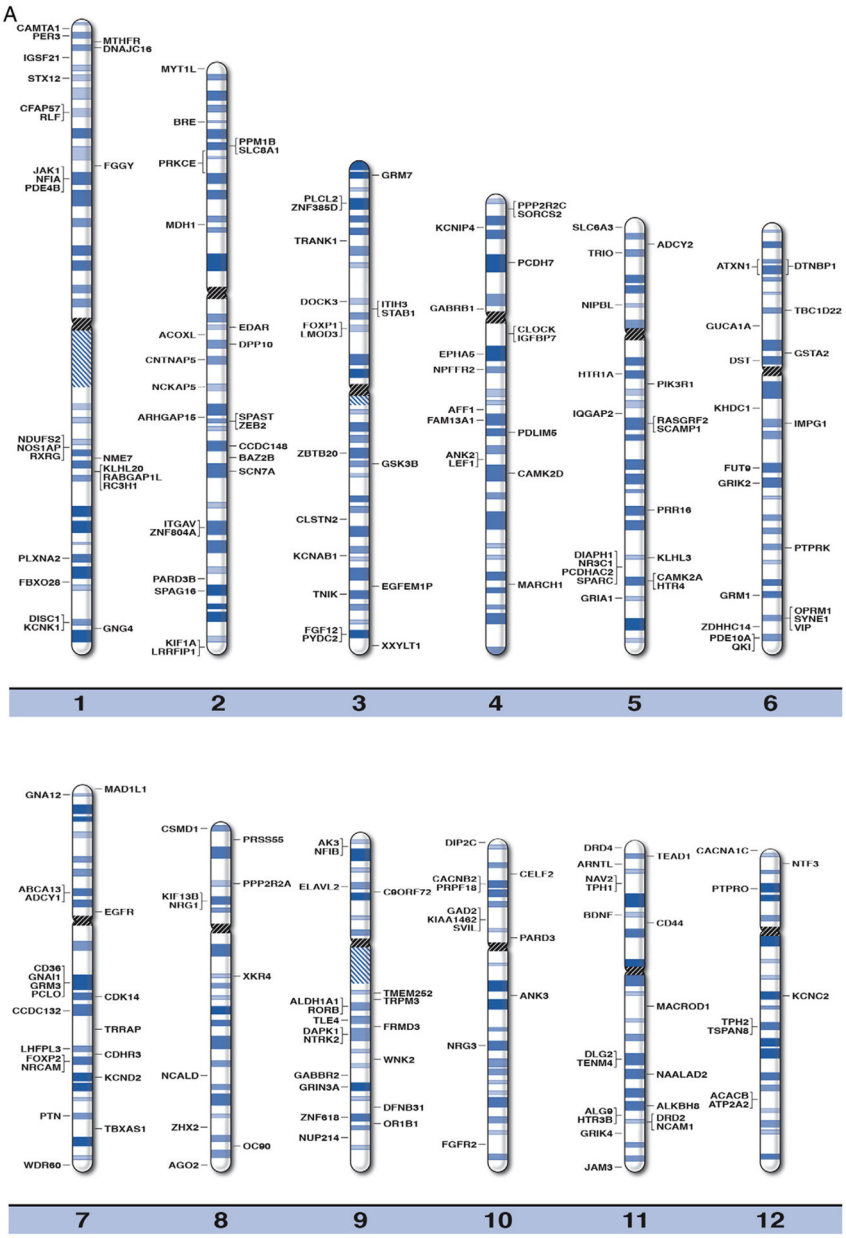

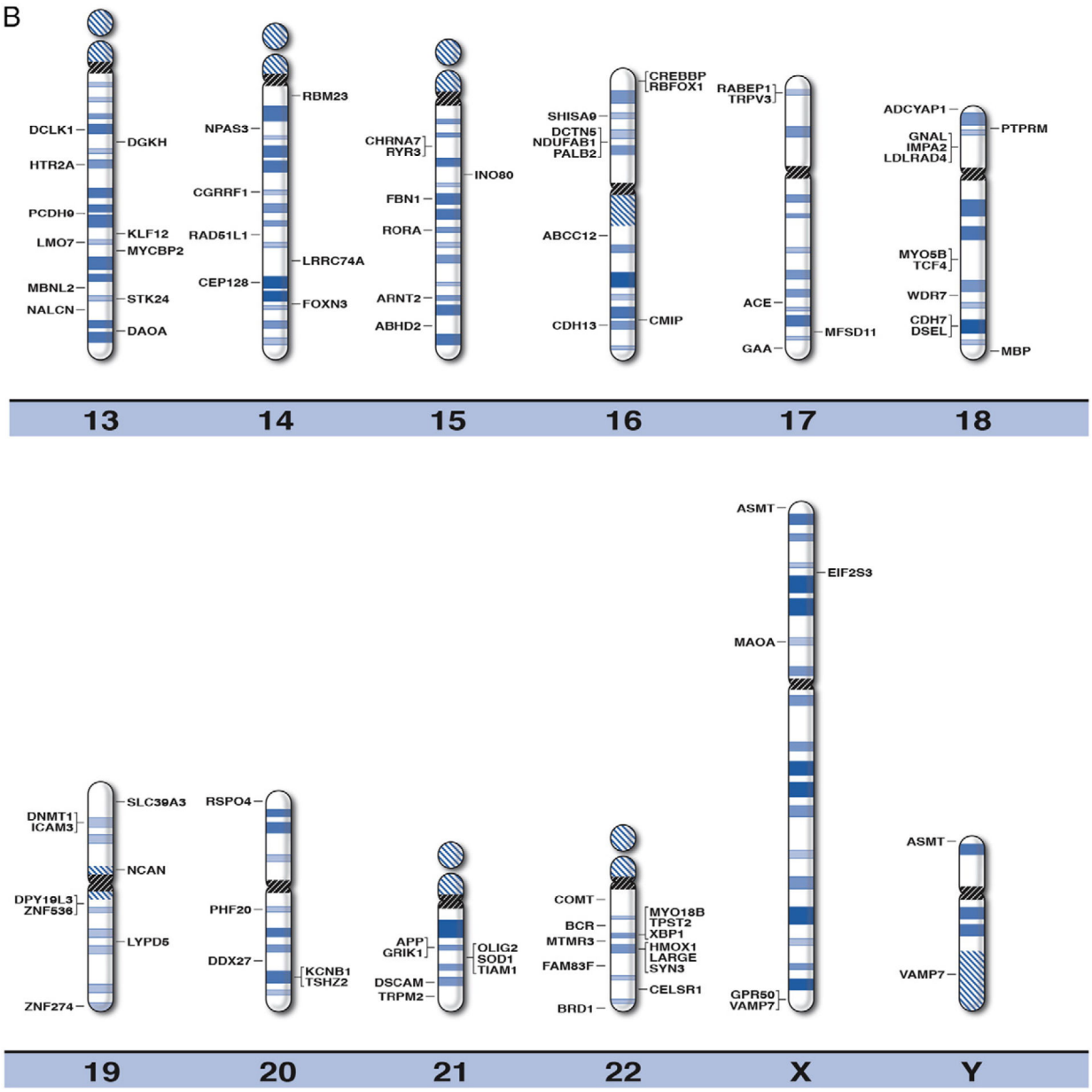

Fig. 1.

High-resolution chromosome ideograms (850 band level) with the BPD gene symbol placed at the chromosomal band location. The centromere area, highlighted in black, separates the upper short “p” arm and the lower long “q” arm for each chromosome. The gene symbols are arranged in alphabetical order with the expanded name and chromosome band position listed in Table 1.

Table 1

Known and candidate genes for bipolar disorder (BPD) and overlap with schizophrenia and autism.

Gene symbol	Gene name	Location	Source
ABCA13[*]	ATP-binding cassette, subfamily A, member 13	*7p12.3F*	Knightet al. (2009)
ABCCl2	ATP-binding cassette, subfamily C, member 12	*16q12.1*	Xu et al. (2014)
ABHD2	Abhydrolase domain containing 2	*15q26.1*	Xu et al. (2014)
ACACB	Acetyl-coenzyme A carboxylase beta	*12q24.11*	Le-Niculescu et al. (2009)
ACE[*]	Angiotensin I converting enzyme	*17q23.3*	Zou et al. (2011)
ACOXL	Acyl-CoA oxidase-like	*2q13*	Xu et al. (2014)
ADCY1[*]	Adenylate cyclase 1 (brain)	*7p12.3*	Le-Niculescu et al. (2009)
ADCY2	Adenylate cyclase 2	*5p15.31*	Mühleisen et al. (2014)
ADCYAP1[*]	Adenylate cyclase activating polypeptide 1 (pituitary)	*18p11.32*	Le-Niculescu et al. (2009)
AFF1	AF4/FMR2 family, member 1	*4q21.3*	Xu et al. (2014)
AGO2	Argonate RISC catalytic component 2	*8q24.3*	Le-Niculescu et al. (2009)
AK3	Adenylate kinase 3	*9p24.1*	Le-Niculescu et al. (2009)
ALDHIAI	Aldehyde dehydrogenase 1 family, member A1	*9q21.13*	Le-Niculescu et al. (2009)
ALG9	ALG9, alpha-1,2-mannosyltransferase	*11q23.1*	Baysal et al. (2002)
ALKBH8	AlkB, alkylation repair homolog 8 (*Escherichia coli*)	*11q22.3*	Xu et al. (2014)
ANK2[#]	Ankyrin 2, neuronal	*4q25*	Le-Niculescu et al. (2009)
ANK3[*#]	Ankyrin 3	*10q21.2*	Takata et al. (2011)
APP[#]	Amyloid beta (A4) precursor protein	*21q21.3*	Le-Niculescu et al. (2009)
ARHGAP15[#]	Rho GTPase activating protein 15	*2q22.2*	Xu et al. (2014)
ARNT2[#]	Aryl-hydrocarbon receptor nuclear translocator 2	*15q25.1*	Xu et al. (2014)
ARNTL[*]	Aryl hydrocarbon receptor nuclear translocator-like	*11p15.3*	Le-Niculescu et al. (2009)
ASMT[#]	Acetylserotonin O-methyltransferase	*Xp22.33 or Yp11.32*	Etain et al. (2012)
ATP2A2	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2	*12q24.11*	Xu et al. (2014)
ATXN1[*]	Ataxin 1	*6p22.3*	Le-Niculescu et al. (2009)
BAZ2B	Bromodomain adjacent to zinc finger domain, 2B	*2q24.2*	Xu et al. (2014)
BCR	Breakpoint cluster region	*22q11.23*	Hashimoto et al. (2005)

Gene symbol	Gene name	Location	Source
CSMD1[*#]	CUB and sushi multiple domains 1	*8p23.2*	Sklar et al. (2008)
DAOA[*]	D-Amino acid oxidase activator	*13q33.2*	Detera-Wadleigh and McMahon (2006)
DAPK1[#]	Death-associated protein kinase 1	*9q21.33*	Le-Niculescu et al. (2009)
DCLK1	Doublecortin-like kinase 1	*13q13.3*	Le-Niculescu et al. (2009)
DCTN5[#]	Dynactin 5 (P25)	*16p12.2*	Burton et al. (2007)
DDX27	DEAD (Asp-Glu-Ala-Asp) box polypeptide 27	*20q13.13*	Xu et al. (2014)
DFNB31	Deafness, autosomal recessive 31	*9q32*	Ollila et al. (2009)
DGKH	Diacylglycerol kinase, eta	*13q14.11*	Baum et al. (2008a, 2008b)
DIAPH1	Diaphanous-related formin 1	*5q31.3*	Le-Niculescu et al. (2009)
DIP2C	Disco-interacting protein 2 homolog C (*Drosophila*)	*10p15.3*	Djurovic et al. (2010)
DISC1 [*#]	Disruption in schizophrenia 1	*1q42.2*	Hodgkinson et al. (2004)
DLG2[*]	Discs, large homolog 2 (*Drosophila*)	*11q14.1*	Xu et al. (2014)
DNAJC16	DnaJ (Hsp40) homolog, subfamily C, member 16	*1p36.21*	Xu et al. (2014)
DNMT1 [*]	DNA methyltransferase 1	*19p13.2*	Veldic et al.(2005)
DOCK3	Dedicator of cytokinesis 3	*3p212*	Baum et al. (2008a, 2008b)
DPP10[*#]	Dipeptidyl-peptidase 10 (non-functional)	*2q14.1*	Le-Niculescu et al. (2009)
DPY19L3	Dpy-19-like 3 (*Caenorhabditis elegans*)	*19q13.11*	Smith et al. (2009)
DRD2[*#]	Dopamine receptor D2	*11q23.2*	Le-Niculescu et al. (2009)
DRD4[*]	Dopamine receptor D4	*11p15.5*	López León et al. (2005)
DSCAM[#]	Down syndrome cell adhesion molecule	*21q22.2*	Xu et al. (2014)
DSEL	Dermatan sulfate epimerase-like	*18q22.1*	Goossens et al. (2003)
DST[#]	Dystonin	*6p12.1*	Le-Niculescu et al. (2009)
DTNBP1[*]	Dystrobrevin binding protein 1	*6p22.3*	Gaysina et al. (2009)
EDAR	Ectodysplasin A receptor	*2q12.3*	Xu et al. (2014)
EGFEM1P	EGF-Like and EMI domain containing 1, pseudogene	*3q26.2*	Xu et al. (2014)
EGFR	Epidermal growth factor receptor	*7p11.2*	Sklaret al.(2008)
EIF2S3[#]	Eukaryotic translation initiation factor 2, subunit 3 gamma, 52 kDa	*Xp22.11*	Cichon et al., (2011)
ELAVL2	ELAV like neuron-specific RNA binding protein 2	*9p21.3*	Le-Niculescu et al. (2009)
EPHA5	EPH receptor 5	*4q13.1*	Le-Niculescu et al. (2009)

Gene symbol	Gene name	Location	Source
FAM13A1	Family with sequence similarity 13, member A	*4q22.1*	Le-Niculescu et al. (2009)
FAM83F	Family with sequence similarity 83, member F	*22q13.1*	Xu et al. (2014)
FBN1	Fibrillin 1	*15q21.1*	Djurovic et al. (2010)
FBXO28	F-Box protein 28	*1q42.11*	Xu et al. (2014)
FGF12	Fibroblast growth factor 12	*3q28*	Cichon et al. (2011)
FGFR2	Fibroblast growth factor receptor 2	*10q26.13*	Xu et al. (2014)
FGGY	FGGY carbohydrate kinase domain containing	*1p32.1*	Kerner et al. (2013)
FRMD3	FERM domain containing 3	*9q21.32*	Djurovic et al. (2010)
FOXN3	Forkhead box N3	*14q32.11*	Baum et al. (2008a, 2008b)
FOXP1[#]	Forkhead box P1	*3p14.1*	Le-Niculescu et al. (2009)
FOXP2[*#]	Forkhead box P2	*7q31.1*	Xu et al. (2014)
FUT9	Fucosyltransferase 9 (alpha (1,3) fucosyltransferase)	*6q16.1*	Le-Niculescu et al. (2009)
GAA	Glucosidase, alpha; acid	*17q25.3*	Le-Niculescu et al. (2009)
GABBR2	Gamma-aminobutyric acid (GABA) B receptor 2	*9q22.33*	Djurovic et al. (2010)
GABRB1[#]	Gamma-aminobutyric acid (GABA) A receptor, beta 1	*4p12*	Burton et al. (2007)
GAD2[*]	Glutamate decarboxylase 2 (pancreatic islets and brain, 65 kDa)	*10p11.23*	Heckers et al. (2002)
GNAI1	Guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1	*7q21.11*	Le-Niculescu et al. (2009)
GNA12	Guanine nucleotide binding protein (G protein) alpha 12	*7p22.2*	Le-Niculescu et al. (2009)
GNAL	Guanine nucleotide binding protein (G protein), alpha activating activity polypeptide, olfactory type	*18p11.21*	Corradi et al. (2005)
GNG4	Guanine nucleotide binding protein (G protein), gamma 4	*1q42.3*	Cichon et al. (2011)
GPR50[*]	G protein-coupled receptor 50	*Xq28*	Thomson et al. (2005)
GRIA1[*]	Glutamate receptor, ionotropic, AMPA1 (alpha 1)	*5q33.2*	Le-Niculescu et al. (2009)
GRIK1	Glutamate receptor, ionotropic, kainate 1	*21q21.3*	Le-Niculescu et al. (2009)
GRIK2[#]	Glutamate receptor, ionotropic, kainite 2	*6q16.3*	Shaltiel et al. (2008)
GRIK4[*]	Glutamate receptor, ionotropic, kainite 4	*11q23.3*	Blackwood et al. (2007)
GRIN3A[*]	Glutamate receptor, ionotropic, N-methyl-D-aspartate 3A	*9q31.1*	Cichon et al. (2011)
GRM1[#]	Glutamate receptor, metabotropic 1	*6q24.3*	Le-Niculescu et al. (2009)
GRM3[*]	Glutamate receptor, metabotropic 3	*7q21.11*	Le-Niculescu et al. (2009)

Gene symbol	Gene name	Location	Source
GRM7[*]	Glutamate receptor, metabotropic 7	*3p26.1*	Burton et al. (2007)
GSK3B[*#]	Glycogen synthase kinase 3 beta	*3q13.33*	Le-Niculescu et al. (2009)
GSTA2	Glutathione S-transferase alpha 2	*6p12.2*	Le-Niculescu et al. (2009)
GUCA1A	Guanylate cyclase activator 1 A	*6p21.1*	Xu et al. (2014)
HMOX1	Heme oxygenase 1	*22q12.3*	Le-Niculescu et al. (2009)
HTR1A[*]	5-Hydroxytryptamine (serotonin) receptor 1A, G protein-coupled	*5q12.3*	Kishi et al. (2011)
HTR2A[*#]	5-Hydroxytryptamine (serotonin) receptor 2A, G-protein-coupled	*13q14.2*	Le-Niculescu et al. (2009)
HTR3B[*]	5-Hydroxytryptamine (serotonin) receptor 3B, ionotropic	*11q23.1*	Hammer et al. (2012)
HTR4[*]	5-Hydroxytryptamine (serotonin) receptor 4, G-protein coupled	*5q32*	Ohtsuki et al. (2002)
ICAM3	Intercellular adhesion molecule 3	*19p13.2*	Cichon et al. (2011)
IGFBP7	Insulin-like growth factor binding protein 7	*4q12*	Xu et al. (2014)
IGSF21	Immunoglobin superfamily, member 21	*1p36.13*	Cichon et al. (2011)
IMPA2[*]	Myo-inositol monophosphatase 2	*18p11.21*	Sjøholt et al. (2004)
IMPG1	Interphotoreceptor matrix proteoglycan 1	*6q14.1*	Xu et al. (2014)
INO80	INO80 complex subunit	*15q15.1*	Xu et al. (2014)
IQGAP2	IQmotif containing GTPase activating protein 2	*5q13.3*	Le-Niculescu et al. (2009)
ITGAV	Integrin, alpha V	*2q32.1*	Le-Niculescu et al. (2009)
ITIH3[*]	Inter-alpha-trypsin inhibitor, heavy chain 3	*3p21.1*	Hamshere et al. (2013)
JAK1	Janus kinase 1	*1p31.3*	Xu et al. (2014)
JAM3	Junctional adhesion molecule 3	*11q25*	Baum et al. (2008a, 2008b)
KCNAB1	Potassium channel, voltage gated subfamily A regulatory beta subunit 1	*3q25.31*	Le-Niculescu et al. (2009)
KCNB1	Potassium channel, voltage gated Shab-related subfamily B, member 1	*20q13.2*	Le-Niculescu et al. (2009)
KCNC2	Potassium channel, voltage gated Shaw related subfamily C, member 2	*12q14.1*	Burton et al. (2007)
KCND2[#]	Potassium voltage-gated channel, Shal-related family, member 2	*7q31.31*	Le-Niculescu et al. (2009)
KCNIP4	Kv channel interacting protein 4	*4p15.32*	Xu et al. (2014)
KCNK1	Potassium channel, subfamily K, member 1	*1q422*	Le-Niculescu et al. (2009)
KHDC1	KH homology domain containing 1	*6q13*	Xu et al. (2014)
KIAA1462	KIAA1462 gene	*10p11.23*	Xu et al. (2014)

Gene symbol	Gene name	Location	Source
KIF13B	Kinesin family member 13B	*8p12*	Xu et al. (2014)
KLF12	Kruppel-like factor 12	*13q22.1*	Le-Niculescu et al. (2009)
KIF1A	Kinesin family member 1 A	*2q37.3*	Le-Niculescu et al. (2009)
KLHL3	Kelch-like family member 3	*5q312*	Cichon et al. (2011)
KLHL20	Kelch-like family member 20	*1q25.1*	Xu et al. (2014)
LARGE	Like-glycosyltransferase	*22q12.3*	Le-Niculescu et al. (2009)
LDLRAD4	Low density lipoprotein receptor class A domain containing 4	*18p11.21*	Le-Niculescu et al. (2009)
LEF1	Lymphoid enhancer-binding factor 1	*4q25*	Le-Niculescu et al. (2009)
LHFPL3	Lipoma HMGIC fusion partner-like 3	*7q22.2*	Cichon et al. (2011)
LMO7	LIM domain 7	*13q22.2*	Le-Niculescu et al. (2009)
LMOD3	Leiomodin 3	*3p14.1*	Xu et al. (2014)
LRRC74A	Leucine rich repeat containing 74A	*14q24.3*	Xu et al. (2014)
LRRFIP1	Leucine rich repeat (In FLII) interacting protein 1	*2q37.3*	Xu et al. (2014)
LYPD5	LY6/PLAUR domain containing 5	*19q13.31*	Cichon et al. (2011)
MACROD1	MACRO domain containing 1	*11q13.1*	Cichon et al. (2011)
MAD1L1[*]	MAD1 mitotic arrest deficient-like 1 (yeast)	*7p22.3*	Cichon et al. (2011)
MAOA[*#]	Monoamine oxidase A	*Xp11.3*	Fan et al. (2010)
MARCH1	Membrane-associated ring finger (C3HC4) 1, E3 ubiquitin protein ligase	*4q32.2*	Xu et al. (2014)
MBNL2	Musclebind-like splicing regulator 2	*13q32.1*	Le-Niculescu et al. (2009)
MBP	Myelin basic protein	*18q23*	Le-Niculescu et al. (2009)
MDH1	Malate dehydrogenase 1, NAD (soluble)	*2p13.3*	Le-Niculescu et al. (2009)
MFSD11	Major facilitator superfamily domain containing 11	*17q25.1*	Xu et al. (2014)
MTHFR[*#]	Methylenetetrahydrofolate reductase (NAD(P)H)	*1p36.22*	El-Hadidy et al. (2014)
MTMR3	Myotubularin related protein 3	*22q12.2*	Xu et al. (2014)
MYCBP2	MYC binding protein 2, E3 ubiquitin protein ligase	*13q22.3*	Le-Niculescu et al. (2009)
MYO5B	Myosin VB	*18q21.1*	Sklar et al. (2008)
MYO18B	Myosin XVIIIB	*22q12.1*	Xu et al. (2014)
MYT1L[#]	Myelin transcription factor 1-like	*2p25.3*	Le-Niculescu et al. (2009)
NAALAD2	N-acetylated alpha-linked acidic dipeptidase 2	*11q14.3*	Xu et al. (2014)
NALCN[*]	Sodium leak channel, non-selective	*13q32.3*	Sklar et al. (2008)

Gene symbol	Gene name	Location	Source
NAV2	Neuron navigator 2	*11p15.1*	Le-Niculescu et al. (2009)
NCALD	Neurocalcin delta	*8q22.3*	Xu et al. (2014)
NCAM1[*]	Neural cell adhesion molecule 1	*11q23.2*	Le-Niculescu et al. (2009)
NCAN	Neurocan	*19p12*	Cichon et al. (2011)
NCKAP5[#]	NCK-associated protein 5	*2q21.2*	Smith et al. (2009)
NDUFAB1	NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1, 8 kDa	*16p12.2*	Burton et al. (2007)
NDUFS2	NADH dehydrogenase (ubiquinone) Fe-S protein 2,49 kDa (NADH-coenzyme Qreductase)	*1q23.3*	Le-Niculescu et al. (2009)
NFIA[#]	Nuclear factor I/A	*1p31.3*	Le-Niculescu et al. (2009)
NFIB	Nuclear factor I/B	*9p24.1*	Le-Niculescu et al. (2009)
NIPBL	Nipped-B homolog (*Drosophila*)	*5p132*	Xu et al. (2014)
NME7	NME/NM23 family member 7	*1q24.2*	Xu et al. (2014)
NOS1AP[*#]	Nitric oxide synthase 1 (neuronal) adaptor protein	*1q23.3*	Xu et al. (2014)
NPAS3[*]	Neuronal PAS domain protein 3	*14q13.1*	Pickard et al. (2009)
NPFFR2	Neuropeptide FF receptor 2 isoform 1	*4q13.3*	Xu et al. (2014)
NR3C1	Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	*5q31.3*	Le-Niculescu et al. (2009)
NRCAM[#]	Neuronal cell adhesion molecule	*7q31.1*	(Le-Niculescu et al., (2009)
NRG1 [*#]	Neuregulin 1	*8p12*	Prata et al. (2009)
NRG3[*]	Neuregulin 3	*10q23.1*	Xu et al. (2014)
NTF3[*]	Neurotrophin 3	*12p13.31*	Cichon et al. (2011)
NTRK2[*]	Neurotrophic tyrosine kinase, receptor, type 2	*9q21.33*	Smith et al. (2009)
NUP214	Nucleoporin 214 kDa	*9q34.13*	Xu et al. (2014)
OC90	Otoconin 90	*8q24.22*	Xu et al. (2014)
OLIG2[*]	Oligodendrocyte lineage transcription factor 2	*21q22.11*	Le-Niculescu et al. (2009)
OPRM1 [#]	Opioid receptor, mu 1	*6q25.2*	Le-Niculescu et al. (2009)
OR1B1	Olfactory receptor, family 1, subfamily B, member 1	*9q33.2*	Xu et al. (2014)
PALB2	Partner and localizer of BRCA2	*16p12.2*	Tesli et al. (2010)
PARD3	Par-3 family cell polarity regulator	*10p11.21*	Le-Niculescu et al. (2009)
PARD3B[#]	Par-3 family cell polarity regulator beta	*2q33.3*	Cichon et al. (2011)

Gene symbol	Gene name	Location	Source
PCDHAC2[#]	Protocadherin-alpha, subfamily C, 2	*5q31.3*	Pedrosa et al. (2008)
PCDH7	Protocadherin 7	*4p15.1*	Le-Niculescu et al. (2009)
PCDH9[#]	Protocadherin 9	*13q21.32*	Le-Niculescu et al. (2009)
PCLO	Piccolo presynaptic cytomatrix protein	*7q21.11*	Choi et al. (2011)
PDE10A	Phosphodiesterase 10 A	*6q26*	Le-Niculescu et al. (2009)
PDE4B[*#]	Phosphodiesterase 4B, CAMP-specific	*1p31.3*	Xu et al. (2014)
PER3[*]	Period circadian clock 3	*1p3623*	Benedetti et al. (2008)
PDLIM5[*]	PDZ and LIM domain 5	*4q22.3*	Shi et al. (2008)
PHF20	PHD finger protein 20	*20q11.22*	Xu et al. (2014)
PIK3R1	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	*5q13.1*	Le-Niculescu et al. (2009)
PLCL2	Phospholipase C-like 2	*3p24.3*	Xu et al. (2014)
PLXNA2[*]	Plexin A2	*1q32.2*	Le-Niculescu et al. (2009)
PPM1B	Protein phosphatase, Mg2+/Mn2+ dependent, 1B	*2p22.1*	Le-Niculescu et al. (2009)
PPP2R2A	Protein phosphatase 2, regulatory subunit B, alpha	*8p212*	Xu et al. (2014)
PPP2R2C	Protein phosphatase 2, regulatory subunit B, gamma	*4p16.1*	Baum et al. (2008a, 2008b)
PRKCE	Protein kinase C, epsilon	*2p21*	Le-Niculescu et al. (2009)
PRPF18	Pre-MRNA processing factor 18	*10p12.33*	Xu et al. (2014)
PRR16	Proline rich 16	*5q23.1*	Xu et al. (2014)
PRSS55	Protease, serine, 55	*8p23.1*	Xu et al. (2014)
PTN	Pleiotrophin	*7q33*	Le-Niculescu et al. (2009)
PTPRK	Protein tyrosine phosphatase, receptor type, K	*6q22.33*	Le-Niculescu et al. (2009)
PTPRM[#]	Protein tyrosine phosphatase, receptor type, M	*18p11.23*	Le-Niculescu et al. (2009)
PTPRO	Protein tyrosine phosphatase, receptor type, O	*12p12.3*	Xu et al. (2014)
PYDC2	Pyrin domain containing 2	*3q28*	Cichon et al. (2011)
QKI[*]	Quaking homolog, KH domain RNA binding	*6q26*	Le-Niculescu et al. (2009)
RABEP1	Rabaptin, RAB GTPase binding effector protein 1	*17p13.2*	Djurovic et al. (2010)
RABGAP1L	RAB GTPase activating protein 1-like	*1q25.1*	Xu et al. (2014)
RAD51B	RAD51, paralog B	*14q24.1*	Xu et al. (2014)
RASGRF2	Ras protein-specific guanine nucleotide-releasing factor 2	*5q14.1*	Le-Niculescu et al. (2009)
RBFOX1[#]	RNA bindingprotein, fox-1 homolog (C. *elegans*) 1	*16p13.3*	Le-Niculescu et al. (2009)

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Gene symbol	Gene name	Location	Source
RBM23	RNA binding motif protein 23	*14q11.2*	Xu et al. (2014)
RC3H1	Ring finger and CCCH-type domains 1	*1q25.1*	Xu et al. (2014)
RLF	Rearranged L-Myc fusion	*1p34.2*	Xu et al. (2014)
RORA#	RAR-related orphan receptor alpha	*15q22.2*	Le-Niculescu et al. (2009)
RORB	RAR-related orphan receptor beta	*9q21.13*	Le-Niculescu et al. (2009)
RSPO4	R-spondin 4	*20p13*	Xu et al. (2014)
RXRG	Retinoid × receptor, gamma	*1q23.3*	Le-Niculescu et al. (2009)
RYR3	Ryanodine receptor 3	*15q13.3*	Le-Niculescu et al. (2009)
SCAMP1	Secretory carrier membrane protein 1	*5q14.1*	Le-Niculescu et al. (2009)
SCN5A#	Sodium channel, voltage gated, type VII alpha subunit	*2q24.3*	Xu et al. (2014)
SHISA9	Shisa family member 9	*16p13.12*	Xu et al. (2014)
SLC39A3	Solute carrier family 39 (Zinc transporter), member 3	*19p13.3*	Baum et al. (2008a, 2008b)
SLC6A3	Solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	*5p15.33*	Greenwood et al. (2006)
SLC8A1	Solute carrier family 8 (sodium/calcium exchanger), member 1	*2p22.1*	Le-Niculescu et al. (2009)
SOD1	Superoxide dismutase 1, soluble	*21q22.11*	Le-Niculescu et al. (2009)
SORCS2	Sortilin-related VPS10 domain containing receptor 2	*4p16.1*	Soronen et al. (2010)
SPAG16	Sperm associated antigen 16	*2q34*	Xu et al. (2014)
SPARC	Secreted protein, acidic, cysteine-rich (osteonectin)	*5q31.3*	Le-Niculescu et al. (2009)
SPAST	Spastin	*2q22.3*	Le-Niculescu et al. (2009)
STAB1	Stabilin 1	*3p21.1*	Baum et al. (2008a, 2008b)
STK24	Serine/threonin kinase 24	*13q32.2*	Le-Niculescu et al. (2009)
STX12	Syntaxin 12	*1p35.3*	Xu et al. (2014)
SVIL	Supervillin	*10p11.23*	Purcell et al. (2009)
SYN3	Synapsin III	*22q12.3*	Le-Niculescu et al. (2009)
SYNE1	Spectrin repeat containing, nuclear envelope 1	*6q252*	Ferreira et al. (2008)
TBC1D22B	TBC1 domain family, member 22B	*6p21.2*	Xu et al. (2014)
TBXAS1	Thromboxane A synthase 1	*7q34*	Xu et al. (2014)
TCF4##	Transcription factor 4	*18q21.1*	Del-Favero et al. (2002)
TEAD1	TEA domain family member 1	*11p15.4*	Xu et al. (2014)
TENM4	Teneurin transmembrane protein 4	*11q14.1*	Sklar et al., 2011

Gene symbol	Gene name	Location	Source
TIAM1	T-cell lymphoma invasion and metastasis 1	*21q22.11*	Le-Niculescu et al. (2009)
TLE4	Transducin-like enhancer ofsplit 4	*9q21.31*	Cichon et al. (2011)
TMEM252	Transmembrane protein 252	*9q21.11*	Xu et al. (2014)
TNIK	TRAF2 and NCK interacting kinase	*3q26.31*	Le-Niculescu et al. (2009)
TPH1	Tryptophan hydroxylase 1	*11p15.1*	Chen et al. (2012)
TPH2[*#]	Tryptophan hydroxylase 2	*12q21.1*	Cichon et al. (2008)
TPST2	Tyrosylprotein sulfotransferase 2	*22q12.1*	Le-Niculescu et al. (2009)
TRANK1	Tetratricopeptide repeat and ankyrin repeat containing 1	*3p22.2*	Mühleisen et al. (2014)
TRIO[#]	Trio rho guanine nucleotide exchange factor	*5p15.2*	Xu et al. (2014)
TRPM2	Transient receptor potential cation channel, subfamily M, member 2	*21q22.3*	McQuillin et al. (2006)
TRPM3	Transient receptor potential cation channel, subfamily M, member 3	*9q21.12*	Le-Niculescu et al. (2009)
TRPV3	Transient receptor potential cation channel, subfamily V member 3	*17p13.2*	Cichon et al. (2011)
TRRAP	Transformation/transcription domain-associated protein	*7q22.1*	Xu et al. (2014)
TSHZ2	Teashirt zinc finger homeobox 2	*20q13.2*	Le-Niculescu et al. (2009)
TSPAN8	Tetraspanin 8	*12q21.1*	Scholz et al. (2010)
VAMP7	Vesicle-associated membrane protein 7	*Xq28 or Yq12*	Saito et al. (2000)
VIP[#]	Vasoactive Intestinal Peptide	*6q252*	Soria et al. (2010)
WDR60	WD repeat domain 60	*7q36.3*	Xu et al. (2014)
WDR7	WD repeat domain 7	*18q21.31*	Xu et al. (2014)
WNK2	WNK lysine deficient protein kinase 2	*9q22.31*	Cichon et al. (2011)
XBP1[*]	X box-binding protein 1	*22q12.1*	Kakiuchi et al. (2003)
XKR4[*]	XK, Kell blood group complex subunit-related family, member 4	*8q12.1*	Djurovic et al. (2010)
XXYLT1	Xyloside xylosyltransferase 1	*3q29*	Xu et al. (2014)
ZEB2[*]	Zinc finger E-box binding homeobox 2	*2q22.3*	Cichon et al. (2011)
ZBTB20[#]	Zinc finger and BTB domain containing 20	*3q13.31*	Xu et al. (2014)
ZDHHC14	Zinc finger, DHHC-type containing 14	*6q25.3*	Le-Niculescu et al. (2009)
ZHX2	Zinc fingers and homeoboxes 2	*8q24.13*	Le-Niculescu et al. (2009)
ZNF274	Zinc finger protein 274	*19q13.43*	Xu et al. (2014)
ZNF385D[*]	Zinc finger protein 385D	*3p24.3*	Xu et al. (2014)
ZNF536	Zinc finger protein 536	*19q13.11*	Djurovic et al. (2010)

Table 2

Distribution of bipolar disorder (BPD) genes among chromosomes.

Chromosome	Total	Proportion of total BPD genes	P arm	Q arm
1	24	8.3%	12	12
2	23	7.9%	6	17
3	18	6.2%	9	9
4	16	5.5%	5	11
5	18	6.2%	4	14
6	18	6.2%	6	12
7	20	6.9%	5	15
8	10	3.4%	5	5
9	19	6.6%	4	15
10	11	3.8%	8	3
11	18	6.2%	7	11
12	8	2.8%	3	5
13	11	3.8%	NA	11
14	7	2.4%	NA	7
15	7	2.4%	NA	7
16	9	3.1%	6	3
17	5	1.7%	2	3
18	11	3.8%	5	6
19	8	2.8%	4	4
20	5	1.7%	1	4
21	7	2.4%	NA	7
22	12	4.1%	NA	12
X	3	1.0%	2	1
Y	0	0.0%	0	0
Both X and Y	2	0.7%	NA	NA
Total	290	100%	94	194

Total number of BPD genes were counted for each chromosome and chromosome arm.

p = short arm; q = long arm.

NA = not applicable due to chromosome structure or location.