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REVIEW

Evidence for single nucleotide polymorphisms and their association with bipolar disorder

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Aleksandra Szczepankiewicz[1,2]

[1]Laboratory of Molecular and Cell Biology, [2]Department of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, Poland

Abstract: Bipolar disorder (BD) is a complex disorder with a number of susceptibility genes and environmental risk factors involved in its pathogenesis. In recent years, huge progress has been made in molecular techniques for genetic studies, which have enabled identification of numerous genomic regions and genetic variants implicated in BD across populations. Despite the abundance of genetic findings, the results have often been inconsistent and not replicated for many candidate genes/single nucleotide polymorphisms (SNPs). Therefore, the aim of the review presented here is to summarize the most important data reported so far in candidate gene and genome-wide association studies. Taking into account the abundance of association data, this review focuses on the most extensively studied genes and polymorphisms reported so far for BD to present the most promising genomic regions/SNPs involved in BD. The review of association data reveals evidence for several genes (*SLC6A4*/*5-HTT* [*serotonin transporter gene*], *BDNF* [*brain-derived neurotrophic factor*], *DAOA* [*D-amino acid oxidase activator*], *DTNBP1* [*dysbindin*], *NRG1* [*neuregulin 1*], *DISC1* [*disrupted in schizophrenia 1*]) to be crucial candidates in BD, whereas numerous genome-wide association studies conducted in BD indicate polymorphisms in two genes (*CACNA1C [calcium channel, voltage-dependent, L type, alpha 1C subunit]*, *ANK3* [*ankyrin 3*]) replicated for association with BD in most of these studies. Nevertheless, further studies focusing on interactions between multiple candidate genes/SNPs, as well as systems biology and pathway analyses are necessary to integrate and improve the way we analyze the currently available association data.

Keywords: candidate gene, genome-wide association study, *SLC6A4*, *BDNF*, *DAOA*, *DTNBP1*, *NRG1*, *DISC1*

Introduction

Bipolar disorder (BD) is a common psychiatric illness characterized by recurrent episodes of mania and depression. Heritability, as calculated in recent twin studies, is estimated at about 85%,[1] which makes BD one of the most heritable multifactorial medical conditions. It is complex in nature, with underlying numerous susceptibility genes as well as environmental risk factors contributing to heterogeneity in observed clinical phenotypes. Over 20 family studies have demonstrated that the relative risk in the first-degree relatives is seven-fold greater than the risk in general population, whereas twin studies have shown a 70% concordance rate in monozygotic twins, indicating that the genetic component is very important in the development of BD. Moreover, family studies have indicated common genetic determinants with other psychiatric disorders such as schizophrenia and autism.[2,3]

In the last decades, genetic studies in BD focused on linkage analyses and association studies of candidate genes, resulting in numerous chromosomal regions and gene

Correspondence: Aleksandra Szczepankiewicz
Laboratory of Molecular and Cell Biology, Department of Psychiatric Genetics, Poznan University of Medical Sciences, 27/33 Szpitalna St, 60-572 Poznan, Poland
Tel +48 61 849 1311
Fax +48 61 848 0111
Email alszczep@ump.edu.pl

polymorphisms linked to the disease. However, the results so far have been inconsistent across the studies, possibly due to differences between the populations analyzed, limited sample sizes with insufficient power to detect an association, as well as different definitions and descriptions used for the diagnosis of clinical phenotype. Recently, genome-wide association studies (GWASs) have also been applied to discover novel candidates and replicate the findings from previous association analyses of single susceptibility genes.

The aim of this review is to summarize the findings from numerous association studies, focusing on variants within genes that have been widely analyzed and replicated or functionally tested for relevance to the BD phenotype.

Candidate gene studies

In this approach, a specific gene based on its function is tested for possible involvement in the pathogenesis of disease. Genetic markers of known function or located in potentially important regulatory gene regions are analyzed in case-control studies to determine if the variant is involved in disease. This method enables the detection of variants of physiological relevance using a limited number of statistical tests; however, it is confined to suspected genes with no possibility of identifying novel candidates. A large number of association studies for candidate genes in BD have been performed so far. Some of the candidate genes associated with BD are presented in Table 1.

However, most of these studies present discrepant findings not replicated by others, which makes the interpretation of data difficult. The most consistent associations were observed for a few candidates: *SLC6A4*/*5-HTT* (*serotonin transporter*), *BDNF* (*brain-derived neurotrophic factor*), *COMT* (*catechol-O-methyltransferase*), *DISC1* (*disrupted in schizophrenia 1,* coding for a neuronal growth-related protein), *DTNBP1* (*dysbindin*), *DAOA* (*D-amino acid oxidase activator*), and *NRG1* (*neuregulin 1*).

SLC6A4/*5-HTT* has been one of the most extensively studied in psychiatric diseases.[4] The transporter plays a crucial role in the active reuptake of serotonin at the synapse that is a known target of selective serotonin reuptake inhibitor antidepressants, which block transporter action. Although numerous studies analyzing its possible association with

Table 1 Candidate genes most studied in association with bipolar disorder

Gene symbol	Gene name	Single nucleotide polymorphisms studied	Result	Reference
5-HTT	*Serotonin transporter*	956304, rs25528, rs6354, rs6355, rs6353, rs6352, rs1042173, rs1532042	Protective haplotype	5
		rs1050565, rs2020934, rs2066713, rs2020936, rs2020937, rs2020938, rs2020939, rs140701, rs3794808, rs3813034	Negative	6–8
BDNF	*Brain-derived neurotrophic factor*	Val/Met (rs6265)	Positive	9–17,25
		Val/Met (rs6265)	18-23	18–23
		rs988748-(GT)n-rs6265; rs1519480, rs12273363, rs11030107; rs1519480, rs7127507 rs2030324, rs2883187	Positive	17,26,27
COMT	*Catechol-O-methyltransferase*	Val/Met	Positive	36,37
		Val/Met	Negative	29–35
		rs737865, rs165688, rs165599, rs2097603	Positive	35,38,39
DISC1	*Disrupted in schizophrenia 1*	rs1407598, rs1407598, rs1535529, rs3524; rs1538977, rs2492367, rs2812393, rs1322784; rs1538979, rs821577; rs766288, rs3738401, rs2492367, rs6675281, rs12133766, rs1000731, rs7546310 and rs821597; rs2738864(C)-rs16841582(C)	Positive	41–46
		A844G, C1348T, C1446T, C1460T, T1595C, C14T, T11870C, G11160A, C11085A, C9481T, G1916A, T2163A, G2304C, C3215T, G65049	Negative	47
DTNBP1	*Dysbindin*	rs2619538; P1757 and P1320; rs3213207, rs1011313, rs2005976, rs760761, rs2619522; P1763	Positive	48–51
DAOA	*D-amino acid oxidase activator*	rs1935058, rs1341402, rs2391191, rs1935062, rs947267, rs954581; M12, rs1341402, M15 (rs2391191), rs1935062, M19 (rs778294), M23, M24; rs746187 (M7), rs3916966 (M13), rs3916972 (M25); rs746187-G and rs3916972-G	Positive	54–58
		Meta-analysis	Negative	59
NRG1	*Neuregulin 1*	SNP8NRG221533, SNP8NRG241930, SNP8 NRG243177 (rs6994992)	Positive	61,62
		SNP8NRG221533, 478B14-878, 420M9–139, SNP8 NRG243177, D8S1810	Negative	63

BD have been performed to date, most of them have focused on the variable number of tandem repeats polymorphism, which has turned out to have functional significance on the transcription initiation of the transporter. Only several association studies including single nucleotide polymorphisms (SNPs) within *5-HTT* have been reported so far, but none of these has shown association with BD.[5–8]

Another candidate gene extensively studied in BD is *BDNF*, a factor involved in brain development – in particular, in the catecholamine system implicated in BD. Its expression is increased on lithium and antidepressant administration. The first described variant includes a functional SNP, Val/Met substitution (rs6265), that affects peptide trafficking and release. Association studies of this functional polymorphism with BD produced inconsistent findings across the populations, with either positive[9–17] or negative results.[18–23] The meta-analysis of this substitution has not confirmed the association with BD.[24] However, another meta-analysis by Fan and Sklar,[25] based on original published association studies between the Val66Met polymorphism and BD, including 14 studies (4,248 cases and 7,080 control subjects and 858 nuclear families), showed modest but significant evidence for the association of this locus with BD. Some association studies of other SNPs within *BDNF* (rs6265, rs1519480, rs12273363, rs11030107, rs11030104, rs11030119; haplotype consisting of rs6265 and rs988748; rs1519480, rs7127507) support their role in the pathogenesis of BD,[17,26,27] but others could not replicate the association of rs6265 and rs11030101 with BD.[23]

COMT is an enzyme involved in monoamine degradation and its gene has been suggested as a candidate for BD.[28] The most studied polymorphism, Val/Met substitution, which has been shown to influence enzyme activity, has not been confirmed to be associated with BD[29–35] except in some studies.[36,37] However, other polymorphisms (rs165599, rs2097603, Val/Met variant, rs737865) were analyzed with positive results for association with BD.[35,38,39]

Some of the important candidate genes (*DISC1*, *DTNBP1*, *DAOA*, *NRG1*) with evidence for association with BD were initially identified by mapping studies in schizophrenia and later also shown to be involved in BD.

DISC1 was identified by mapping a balanced translocation between chromosome 1 and 11 that was found to segregate with both schizophrenia and BD in a large Scottish pedigree and was the causative mutation in the family.[40] Further studies supported the association of this gene with BD, both single markers (rs6675281; rs1538979, rs821577; 1030711; rs2492367, rs7546310) and haplotypes (rs7546310A-rs82159T; rs766288A-rs2492367C; rs1000731A-rs7546310C, rs2738864C-rs16841582C; rs1030711A-rs751229C-rs1285730A-rs3738401G),[41–46] except the study by Devon et al,[47] in which no association of *DISC1* polymorphisms (A844G, C1460T, T2163A, and T11870C) with BD was reported.

DTNBP1 is another candidate gene that was reported initially for schizophrenia but has also shown association with BD. The protein is expressed in all neuronal populations of the hippocampus and plays a role in glutamatergic pathway signaling. The association of single polymorphisms (rs2005976, rs760761; rs2619522) and haplotypes (rs3213207A-rs1011313C-rs2005976G-rs760761T-rs2619522A; TCGG and GTAA of SNPs: rs2619522, rs760761, rs2005976, rs2619528; rs2619538-rs2619522) has been supported by several positive studies.[48–51]

DAOA (G72/G30) was first identified by linkage family studies to chromosome 13q, a region also linked to BD.[52,53] A number of studies showed positive association with BD (rs1935058; rs1341402, rs1935062, rs778294; rs947267; haplotypes: rs2111902A-rs3918346T and rs746187G-rs3916972G; haplotypes: CGCAT, TAACT, CGACT, TGCAT of five SNPs: rs1935058, rs2391191, rs1935062, rs947267, rs954581).[54–57] Further evidence was reported in a large study analyzing nine polymorphisms that tag the common genetic variations in *DAOA* in association with susceptibility to mood episodes in BD (rs391695, rs1341402, DAOA_3′UTR_SNP12).[58] However, associations of the studied *DAOA* polymorphisms (rs2391191G, rs778294T, rs1341402T, rs1935058C, and rs1935062C) were not confirmed in a meta-analysis by Shi et al.[59]

NRG1 interacts with ErbB4 to regulate glutamate signaling via the N-methyl-D-aspartate receptor. The gene was first identified by linkage to chromosome 8p in Icelandic families with schizophrenia,[60] followed by association of this gene with BD (single markers: SNP8NRG221533; rs553950, rs327329, rs7007662; haplotypes: NP8NRG221533-rs4298458-SNP8NRG241930-SNP8NRG243177; rs2919390-rs6988339-rs3757930).[61,62] However, this was not replicated in an Irish trios study (SNP8NRG221533, 478B14-878, 420M9-139, SNP8NRG243177).[63]

GWASs

This method involves the simultaneous analysis of hundreds of SNPs distributed throughout the genome in large cohorts of patients and controls to identify genetic markers associated with the disease. In contrast to most candidate gene studies, GWASs are well powered and the genes found are usually replicated in other studies, demonstrating their priority over candidate gene studies. In BD, the first such study was published by the Wellcome Trust Case Control

Consortium (WTCCC) in 2007. The study included about 2,000 bipolar cases and 3,000 controls and analysis of 500,000 SNPs revealed that the region with the strongest evidence for association with BD was at locus 16p12 (P=10^{-8}), which contains three genes of potential pathological relevance to BD (*PALB2 [partner and localizer of BRCA2], NDUFAB1 [NADH dehydrogenase (ubiquinone) 1], DCTN5 [dynactin 5]*).[41] Another GWAS was performed by Sklar et al[64] on the sample for the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a large treatment study in BD. This analysis identified two genes, *MYO5B* (*myosin 5B*) and *TSPAN8* (*tetraspanin-8*), associated with BD, although this finding was not replicated in an independent sample.

The gene that showed evidence for association in both those studies was *CACNA1C*, a member of a family of L-type calcium channels. This candidate gene was also identified in a combined analysis study, by Ferreira et al,[65] of the two aforementioned datasets and additional samples for a total of 4,387 cases and 6,209 controls. This study also identified another candidate with the strongest evidence for association with BD: the *ANK3* (*ankyrin 3*) gene encoding ankyrin G, a cytoskeletal protein expressed in the brain and involved in attaching sodium channels to the cytoskeleton.

A later GWAS performed by Smith et al[66] of a National Institute of Mental Health (NIMH) Genetics Initiative for Bipolar Disorder sample, a part of the Bipolar Genome Study (BiGS), failed to identify any SNP with a genome-wide significance; however, they showed suggestive evidence for association of the following candidate genes: *NAP5 (NCK-associated protein 5)*, *DPY19L3 (dpy-19-like 3 [Caenorhabditis elegans])*, and *NTRK2 (neurotrophic tyrosine kinase receptor type 2)*. In particular, the latter gene is a good candidate, encoding the Trkb tyrosine kinase receptor for BDNF that has been extensively studied in psychiatric disorders. The study by Smith et al is also one of the few that has examined a non-Caucasian population. Combined analysis of European-American and African-American samples enabled identification of several genes showing association in both populations, but with different alleles (*ROR1 [receptor tyrosine kinase-like orphan receptor 1]*, *RGS5 [regulator of G protein signaling 5]*, *BTBD16 [BTB (POZ) domain containing 16]*), suggesting that alternative variants in the same genes predispose to BD depending on the population.

Similar to this study, no significant evidence for association was observed in a GWAS by Scott et al[67] in three populations of 3,683 Caucasian cases and 14,507 controls. The SNPs with suggestive evidence for association included the following genes: *ITIH1 (inter-alpha-trypsin inhibitor heavy chain 1), GNL3 (guanine nucleotide binding protein-like 3), NEK4 (NIMA-related kinase 4)*, and *ITIH3 (inter-alpha-trypsin inhibitor heavy chain 3)*, as well as replication for *ANK3* gene.

A later study undertaken by the Psychiatric GWAS Consortium Bipolar Disorder Working Group[68] published a combined GWAS of 11,974 bipolar patients and 51,792 controls as part of the Psychiatric GWAS Consortium. In that study, genome-wide significant evidence of association for *CACNA1C* was confirmed and for the identification of a new intronic variant in *ODZ4* gene presented.

A novel genetic variation (rs1064395) within the *NCAN* (*neurocan*) gene that showed genome-wide significant association (P=3.02×10^{-8}) was identified in a combined GWAS and first follow-up step study performed in 2,411 BD patients and 3,613 controls.[69] This finding was replicated in a second follow-up step study (6,030 patients and 31,749 controls; P=2.74×10^{-4}). The combined analysis of all study samples yielded a P-value of 2.14×10^{-9}, providing evidence that rs1064395 is a common risk factor for BD. *NCAN* encodes neurocan, an extracellular matrix glycoprotein involved in cell adhesion and migration, with expression localized within cortical and hippocampal areas involved in cognition and emotion regulation implicated in BD.

The most recent GWAS by Green et al[70] of an independent UK sample of 1,218 BD cases and 2,913 controls replicated previous findings by Ferreira et al[65] for two of the three most strongly associated chromosomal regions in the study, *CACNA1C* (rs1006737, P=4.09×10^{-4}) and 15q14 (rs2172835, P=0.043), but not *ANK3* (rs10994336, P=0.912). Moreover, the authors performed combined analysis of two populations, ImmunoChip data (569 quasi-independent SNPs from the 3,016 SNPs genotyped) with the recently published Psychiatric Genome-Wide Association Study Consortium Bipolar Disorder Working Group (PGC-BD) meta-analysis data and found two novel variants associated with BD: rs7296288 (P=8.97×10^{-9}), an intergenic polymorphism on chromosome 12 located between *RHEBL1 (Ras homolog enriched in brain like 1)* and *DHH (desert hedgehog)*, and rs3818253 (P=3.88×10^{-8}), an intronic SNP on chromosome 20q11.2 in the *TRPC4AP (transient receptor potential cation channel, subfamily C, member 4 associated protein)* gene, which lies in a high linkage disequilibrium region along with the genes *GSS (glutathione synthetase)* and *MYH7B (myosin heavy chain 7B)*.

A few national GWASs have also been performed. Among others, one in a Bulgarian population[71] and two in Scandinavian populations – one Swedish[72] and the other Norwegian – followed by replication in an Icelandic population;[73] all of these failed to identify any locus of genome-wide significance for association with BD. However,

in the Bulgarian study, the authors mentioned three variants with possible involvement in BD: rs8099939 (P=2.12×10^{-6}) in the *GRIK5 (glutamate receptor, ionotropic, kainate 5)* gene, rs6122972 (P=3.11×10^{-6}) in the *PARD6B (par-6 family cell polarity regulator beta)* gene, and rs2289700 (P=9.14×10^{-6}) in the *CTSH (cathepsin H)* gene.[71]

Two GWASs in Asian populations have been performed: one by Hattori et al[74] in a Japanese population of 107 cases and 107 controls, and the other by Lee et al[75] in a Han Chinese population of 1,000 bipolar I patients and 1,000 controls. In both studies, none of the SNPs was associated with BD at genome-wide significance. A summary of GWASs is presented in Table 2.

Recently, the Cross-Disorder Group of the Psychiatric Genomics Consortium published GWAS results for five major psychiatric disorders – autism spectrum disorder, attention deficit-hyperactivity disorder, BD, major depressive disorder, and schizophrenia – to identify loci shared between those disorders.[76] The analysis of 33,332 cases and 27,888 controls revealed that genome-wide significance (P<5×10^{-8}) was reached for regions on chromosomes 3p21 and 10q24 and SNPs within two L-type voltage-gated calcium-channel subunits, *CACNA1C* and *CACNB2 (calcium channel, voltage-dependent, beta 2 subunit)*, indicating that specific SNPs are associated with a range of psychiatric disorders and that variation in calcium-channel activity genes may exert pleiotropic effects on the psychopathology of psychiatric genetics.

The results from GWASs provide numerous SNPs evidenced for association with BD, with the strongest confirmation of two loci, *CACNA1C* and *ANK3*. However, lack of consistent findings throughout the studies, possibly due to insufficient power to detect associations with genes of small effects, impede drawing conclusions. Recently, a meta-analysis of GWASs and all published candidate gene-association studies of BD (a total of 487 articles) was published to evaluate the cumulative evidence of associations observed so far.[77] Polymorphisms in *BDNF*, *DRD4, DAOA*, and *TPH1 (tryptophan hydroxylase 1)* were found to be nominally

Table 2 Genome-wide association studies (GWASs) in bipolar disorder

Sample	Population	Type	Sample size	Result	Study
WTCCC	Caucasian	Case control	2,000/3,000	16p12 (*PALB2*)	41
STEP-BD	Caucasian	Case control	1,461/2,008	rs4939921 (*MYO5B*) rs1705236 (*TSPAN8*)	64
WTCCC + STEP-BD	Caucasian	Meta-analysis	4,387/6,209	rs1006737 (*CACNA1C*) rs10994336 (*ANK3*)	65
BiGS (NIMH)	European-American	Case control	1,001/1,033	rs5907577 (*Xq27.1*) rs10193871 (*NAP5*)	66
	African-American	Case control	345/670	rs2111504 (*DPY19L3*) rs2769605 (*NTRK2*)	66
NIMH/Pritzker GSK WTCCC	Caucasian	Pooling; individual genotyping	3,683/14,507	1p31.1 3p21 MCTP1 rs1042779 (*ITIH1*)	67
GWAS Consortium Bipolar Disorder Working Group	Caucasian		11,974/51,792	rs4765913 (*CACNA1C*) rs12576775 (*ODZ4*)	68
German sample, Replication I and II	Caucasian	Case-control pooling	8,441/35,362	rs1064395 (*NCAN*)	69
UK sample ImmunoChip data + PGC-BD	Caucasian	Case control; Meta-analysis	1,218/2,913	rs1006737 (*CACNA1C*) rs2172835 (*15q14*) rs7296288 (between *RHEBL1* and *DHH*) rs3818253 (*TRPC4AP*)	70
Bulgarian	Caucasian	Case control	188/376	rs8099939 (*GRIK5*) rs6122972 (*PARD6B*) rs2289700 (*CTSH*)	71
Swedish	Caucasian	Case control	836/2,093	None	72
Norwegian Icelandic	Caucasian	Case control	194/336 435/10,258	rs4377455 (*BMS3*)	73
Japanese	Asian	Case control	107/107	None	74
Han Chinese	Asian	Case control	1,000/1,000	rs2709736, rs8040009 (*ST8SIA2*) rs2073831 (*KCTD12*) rs11013860 (*CACNB2*)	75

Abbreviations: BiGS, Bipolar Genome Study; GSK, GlaxoSmithKline; NIMH, National Institute of Mental Health; PGC-BD, Psychiatric Genome-Wide Association Study Consortium Bipolar Disorder Working Group; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder; WTCCC, Wellcome Trust Case Control Consortium.

significant; however, none of these findings was significant after correction for multiple testing. Moreover, none of these polymorphisms was significant in the Psychiatric GWAS Consortium Bipolar Disorder study.[76]

Phenotypes related to BD

Taking into account the genetic heterogeneity of BD, it has been suggested that clinical phenotypes may be more useful in delineating the genetic variants contributing to BD than standard diagnostic models.[78] Clinical sub-phenotypes of BD may identify more homogeneous subsets of patients who can be studied with increased power to detect genetic variation. To date, several studies have applied this concept to data from GWASs.

In a GWAS of BD patients with seasonal patterned mania (seasonal or non-seasonal patterned manic episodes), the most significant association was observed for rs41350144, which lies within an intron of the *NF1A (nuclear factor I/A)* gene on 1p31 (P=3.08×10^{-7}), suggesting it may predispose to this subtype of BD.[79]

A GWAS of mood-incongruent psychotic features in bipolar patients (2,196 cases with mood-incongruent psychotic features and 8,148 controls) revealed no association of genome-wide significance; however, several regions with suggestive evidence of association (P<10^{-6}) were found: 6q14.2 within the *PRSS35 (protease serine 35)/SNAP91* (*synaptosomal-associated protein*) gene complex (rs1171113, P=9.67×10^{-8}), 3p22.2 downstream of *TRANK/LBA1 (tetratricopeptide repeat and ankyrin repeat containing 1)* (rs9834970, P=9.71×10^{-8}), and 14q24.2 in an intron of *numb* homolog (*Drosophila*) (rs2333194, P=7.03×10^{-7}).[80]

In a GWAS of factor dimensions in 927 clinically well-characterized BD patients of German ancestry, the authors found that the factor dimension "negative mood delusions" was significantly associated with one variant (rs9875793; n=927; P=4.65×10^{-8}).[81] This SNP is located in an intergenic region of 3q26.1 in the proximity of the *SLC2A2* (*solute carrier family 2* [*facilitated glucose transporter*], *member 2*) gene. In case-control analyses, significant association with the G allele of rs9875793 was only observed in the subgroup of 89 BD patients who displayed symptoms of negative mood delusions. Further support for the association of rs9875793 with BD in patients displaying the negative mood delusions symptom was obtained from an European-American sample of 1,247 BD patients and 1,434 controls.

The study that first tested bipolar patients according to age-at-onset (AAO) subgroups was performed by Dizier et al[82] in a sample of 443 unrelated bipolar patients and 1,731 controls. The study provided evidence for genetic variation within the *ADRB2* (β_2*-adrenoreceptor*) gene region that is specifically associated with the early onset form of BD. However, this finding could not be replicated in the WTCCC sample due to poor genotyping coverage of the *ADRB2* gene (the SNPs that showed the strongest signal for association in the study were not available in the WTCCC sample and were not in LD (linkage disequilibrium) with the SNPs available in the replication sample). Therefore, the finding requires further investigation.

A meta-analysis of two widely studied sub-phenotypes of BD, AAO and psychotic symptoms, which are familial and clinically significant, was conducted by Belmonte Mahon et al[83] on combined data from three GWASs: the NIMH Bipolar Disorder Genetic Association Information Network (GAIN-BP), NIMH BiGS, and a German sample, with a total of 2,836 BD cases with information on sub-phenotypes and 2,744 controls. No SNP reached genome-wide significance for either sub-phenotype. The same results were observed in a meta-analysis with an independent replication sample. This indicates that AAO and psychotic symptoms in BD may be influenced by other variants not measured well by SNP arrays, such as rare alleles.

Family and twin studies suggest that susceptibility for suicide attempts is heritable and distinct from mood disorder susceptibility, and the high resolution of the GWAS approach facilitates the detection of risk loci. The first GWAS performed for lifetime suicide attempts sub-phenotype was conducted by Perlis et al.[84] BD subjects were drawn from the Systematic Treatment Enhancement Program for Bipolar Disorder cohort, the WTCCC bipolar cohort, and the University College London cohort. Replication was pursued in the NIMH Genetic Association Information Network BD project and a German clinical cohort. The strongest evidence of association for suicide attempts in BD was observed in a region without identified genes (rs1466846) and five loci showed suggestive evidence of association.

Another attempted suicide GWAS that compared the SNP genotypes of 1,201 BD subjects with a history of suicide attempts to the genotypes of 1,497 BD subjects without a history of suicide attempts was performed by Willour et al.[85] The authors found 2,507 SNPs with evidence for association with suicide attempts at P<0.001, but these associations were not significantly associated in the replication sample after correcting for multiple testing. However, the combined analysis of the two sample sets produced an association signal on 2p25 (rs300774) at the threshold of genome-wide significance (P=5.07×10^{-8}). This variant is located in a large linkage disequilibrium block containing the *ACP1* (*acid phosphatase 1*) gene, the expression of which

is significantly elevated in BD subjects who have completed suicide. The results of both GWASs suggest that inherited risk for suicide among bipolar patients is unlikely to be the result of individual common variants of large effects.

A GWAS testing comorbidities in BD (BD with psychosis and/or substance abuse in the absence of alcohol dependence) showed association with the rare variant (rs1039002) in the vicinity of the *PDE10A* (*phosphodiesterase 10A*) gene ($P=1.7\times10^{-8}$), which was implicated in the pathophysiology of psychosis. Another rare variant, rs12563333 on chromosome 1q41 close to the *MARK1* (*MAP/microtubule affinity-regulating kinase 1*) gene, demonstrated an almost genome-wide level of significance in this subgroup ($P=5.9\times10^{-8}$). Homozygotes for the minor allele were present in cases and absent in controls. BD with alcohol dependence and other comorbidities was associated with SNP rs2727943 ($P=3.3\times10^{-8}$) on chromosome 3p26.3 located between the genes *BIG-2* (*contactin-4 precursor*) and *CNTN6* (*contactin 6*). BD with low probability of comorbid conditions did not show significant associations.[86]

Neuroimaging is commonly used to characterize brain activity that is altered in psychiatric disorders including BD. By use of functional magnetic resonance imaging, it was found that amygdala activation during a face-processing task differs between bipolar patients and healthy controls.[87] In a GWAS, a SNP (rs2023454) in *DOK5 (docking protein 5)* gene involved in the neurotrophin signaling pathway was found to be associated with right amygdala activation.[88] Another GWAS performed on neurocognition in 157 BD patients and 353 controls[89] identified three intronic SNPs in the *PTPRO (protein tyrosine phosphatase receptor type O)* gene associated with learning and memory (rs17222089, rs11056571, and rs2300290) and rs719714 near *WDR72 (WD repeat domain 72)* associated with executive functioning as well as highly significant interaction between *FOXQ1 (forkhead box Q1)* and *SUMO1P1 (SUMO1 pseudogene 1)* SNPs for psychomotor speed.

Several studies analyzing the influence of variation in candidate genes for BD on neuroanatomy and neurocognition have also been performed. A SNP in the *CACNA1C* gene (rs1006737) previously associated with BD in several GWASs, was also found related to alterations in structural and functional magnetic resonance imaging, with A allele associated with increased gray-matter volume and reduced functional connectivity within the cortico-limbic frontotemporal neural system,[90] as well as worsened performance of executive function tests in BD patients.[91] However, it was not associated with spatial working memory in BD patients.[92] Evidence for the involvement of SNPs within the *DISC1* gene, another strong candidate for BD, in neuroanatomy and neurocognition was provided by Carless et al.[93] Recently, a study by Li et al[94] analyzing SNPs in *CREB1 (cAMP responsive element binding protein 1)* gene in BD patients of European ancestry, reported a significant association of risk SNPs with a decreased hippocampal volume and diminished activation of the left hippocampus, further suggesting their involvement in BD susceptibility.

Conclusion

The results from candidate gene association studies and GWASs have provided some findings for BD and indicated a number of genes and variants involved. However, inconsistency between studies, as well as only modest replication of variants identified for BD by independent analyses – in particular, in the case of candidate gene studies – impede drawing conclusions. The discrepancies in candidate gene studies may partly result from the clinical and genetic heterogeneity of BD and its complex inheritance model but also from methodological issues such as the definition of clinical phenotype.

Further, it should also be taken into account that although many genes/risk alleles are implicated in BD, the individual effect sizes of each allele contribute to only a small fraction (~3%) of the total population variance.[95] Despite the high estimated heritability of BD, the thousands of markers analyzed by GWASs explain only about 5% of phenotypic variance, despite studies of tens of thousands of people. As such, much of the heritability of BD has been missed by GWAS findings so far. The possible explanations of this missing heritability include analysis of rare variants (according to the "common disease-multiple rare variants" hypothesis); analysis of structural genomic variants, termed "copy number variants," with higher odds ratios than common variants (SNPs); as well as the functional characterization of specific SNPs, such as their effects on gene expression or DNA methylation. Next-generation sequencing offers help in elucidating if the missing heritability is due to missed genetic associations. Moreover, taking into account the polygenic inheritance of BD, with a large number of markers with small individual effects collectively accounting for disease risk, novel approaches including systems biology and pathway analysis may be helpful in identifying functional interactions between multiple genes involved in the pathophysiology of BD. These methods are already being used in ongoing experiments[96–98] to determine the underlying mechanisms and identify causal variants for this disease.

Thus, the genetic findings in BD, although promising, are far from being translated into clinical practice.

Disclosure

The author declares no conflicts of interest in this work.

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