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SYSTEMATIC REVIEW

Clinical characteristics indexing genetic differences in bipolar disorder – a systematic review

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Bipolar disorder is a heterogenous condition with a varied clinical presentation. While progress has been made in identifying genetic variants associated with bipolar disorder, most common genetic variants have not yet been identified. More detailed phenotyping (beyond diagnosis) may increase the chance of finding genetic variants. Our aim therefore was to identify clinical characteristics that index genetic differences in bipolar disorder.

We performed a systematic review of all genome-wide molecular genetic, family, and twin studies investigating familial/genetic influences on the clinical characteristics of bipolar disorder. We performed an electronic database search of PubMed and PsycInfo until October 2022. We reviewed title/abstracts of 2693 unique records and full texts of 391 reports, identifying 445 relevant analyses from 142 different reports. These reports described 199 analyses from family studies, 183 analyses from molecular genetic studies and 63 analyses from other types of studies. We summarized the overall evidence per phenotype considering study quality, power, and number of studies.

We found moderate to strong evidence for a positive association of age at onset, subtype (bipolar I versus bipolar II), psychotic symptoms and manic symptoms with familial/genetic risk of bipolar disorder. Sex was *not* associated with overall genetic risk but could indicate qualitative genetic differences. Assessment of genetically relevant clinical characteristics of patients with bipolar disorder can be used to increase the phenotypic and genetic homogeneity of the sample in future genetic studies, which may yield more power, increase specificity, and improve understanding of the genetic architecture of bipolar disorder.

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INTRODUCTION

Bipolar disorder is a psychiatric disorder with heritability estimated at 60–85% [1–3], meaning that genes play an important role in its etiology. Clarifying the genetic architecture of bipolar disorder is crucial to better understand biological pathways leading to the disorder and identify new targets for treatment and prevention. Although major progress has been made in identifying genetic risk variants and understanding its genetic architecture, most common genetic variants have not yet been identified [4]. The largest genome-wide association study to date including more than 40,000 cases with bipolar disorder found 64 genome-wide independent variants and a SNP-heritability of 18.6% [5]. This is substantially fewer than the number of genetic variants expected to be relevant for bipolar disorder: it is estimated that more than 8000 variants will need to be identified to explain 90% of its SNP-heritability [5].

Deep phenotyping – the precise and comprehensive analysis of phenotypic characteristics [6, 7] – is one strategy to increase the chances of identifying relevant genetic variants. Deep phenotyping is likely to be especially relevant for disorders with a varied clinical presentation, such as bipolar disorder. Patients with bipolar disorder can vary considerably, for instance in terms of cycling pattern, response to lithium, or age at onset [4]. For a better understanding of the genetic architecture of bipolar disorder, the collection of phenotypic information beyond just the diagnosis is needed because there may not be a sufficient relationship with any biological process if we only consider the diagnosis [8]. The assessment of genetically relevant clinical characteristics of patients with bipolar disorder can be used to increase the phenotypic and genetic homogeneity of the sample, which may yield more power, increase specificity, and improve understanding of its genetic architecture [8, 9]. For example, several previous studies suggest that the distinction between the subtypes bipolar I and bipolar II is genetically relevant, in terms of differences in overall heritability and genetic correlations with other psychiatric disorders [5, 10]. The value of deep phenotyping for genetic discovery has been illustrated in major depressive disorder in which this approach contributed to the identification

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of the first significant GWAS hits in a relatively small sample [11] and to the discovery that different subtypes of major depression have distinct polygenic profiles [12]. However, there are numerous potentially relevant clinical characteristics in patients with bipolar disorder and assessing all of them is not feasible in large-scale genetic studies. Deep phenotyping in these studies therefore requires a choice regarding which characteristics to measure.

It is currently unclear which clinical characteristics index genetic differences between bipolar disorder patients, as no systematic reviews on this question exist. Previous reviews summarizing evidence from family and twin studies suggested that characteristics such as an early age at onset, psychotic symptoms and response to lithium may be indices of a higher genetic risk of bipolar disorder [13, 14], but these reviews were not systematic and did not include the latest studies including large-scale molecular-genetic studies. A recent systematic review of studies specifically investigating familial co-aggregation of phenotypes among affected relatives was limited by a small number of studies, but found some evidence that several phenotypes, including age at onset, psychotic symptoms, and lithium response, were correlated among affected relatives [15]. This suggests that these phenotypes may index modifier genes - genes that modify the clinical features of a disorder without necessarily causing it [16]. Recently we performed a systematic review to identify clinical characteristics indexing genetic risk for schizophrenia [17]. We summarized evidence from >800 analyses in patients with schizophrenia and other non-affective psychoses, and we found moderate to strong evidence that early age at onset, negative symptoms, chronicity, functional impairment, and female gender indicated a higher familial risk of schizophrenia. The current study performs a similar systematic review for bipolar disorder. Thus, this study summarizes all the available evidence from molecular genetic, family, and twin studies in order to identify phenotypes that index familial/genetic risk of bipolar disorder and phenotypes that index modifier genes.

METHODS

Systematic review design

We used similar methods in this systematic review, as we used in our previous systematic review about clinical characteristics indexing genetic differences in schizophrenia [17].

Eligibility criteria

Studies were eligible for inclusion in this systematic review if they contained analyses that investigated the genetic relevance of phenotypic features in subjects with bipolar disorder. We included studies in which at least 50% of individuals had a diagnosis of a bipolar disorder or related conditions, i.e. bipolar I/II, bipolar spectrum conditions, schizoaffective disorder (bipolar type or mixed type). Because our purpose was to identify phenotypes that could be assessed in patients with bipolar disorder in future large-scale genetic studies, we focused on phenotypic features that can be measured in a clinical or research interview, or with commonly used laboratory or psychometric assessments. Analyses involving measures which required specialized technology such as brain imaging or electrophysiologic measures were excluded.

Relevant analyses investigated whether phenotypic variation measured in patients with bipolar disorder was associated with genome-wide genetic variation. Genome-wide genetic variation could be measured directly using molecular methods (e.g. GWAS, whole-exome or whole-genome sequencing or genome-wide CNV microarrays) or indirectly through patterns of aggregation within families or twin pairs. We excluded candidate gene and linkage-based analyses given low reproducibility [18] as well as genome-wide studies that did not include an omnibus measure of genetic risk such as a polygenic risk score. We set a minimum sample size for inclusion at 50 probands for family studies and 100 probands for molecular-genetic studies. We provided a detailed overview of our inclusion and exclusion criteria in the Supplementary Material.

Included studies fell into 5 main categories:

1. Polygenic risk score (PRS)-based studies– investigate whether the presence of a phenotype in a proband is associated with differences in PRS.
2. Other molecular-genetic studies- investigate whether the presence of a phenotype in a proband is associated with other genome-wide differences e.g., copy number variant (CNV) burden or a higher SNP-based heritability.
3. Studies of familial aggregation – investigate whether the presence of a phenotype in a proband is associated with differences in familial risk for bipolar disorder.
4. Affected relative pair studies – investigate whether a phenotype is correlated among two family members affected with bipolar disorder.
5. Genetic modelling studies – investigate heritability of a phenotype within multiplex families or concordant (and non-concordant) twin pairs.

Genetic modelling studies that properly accounted for affected status could include a majority of non-affected participants, as these genetic models provide results that are informative about the genetic relevance of phenotypic heterogeneity *among* subjects with bipolar disorder and can additionally use non-affected participants to model the genetic correlation between specific phenotypes and the liability to bipolar disorder itself. However, we excluded other studies in which phenotypic variation was measured primarily in individuals without bipolar disorder and that did not apply such genetic models. This includes classic "endophenotype" studies [19] that explore group phenotypic differences in means between cases, unaffected family members of cases, and unrelated controls, as well as studies that correlated a particular phenotype in affected probands and their unaffected relatives. These studies do not investigate whether a particular phenotype is genetically relevant *within* subjects affected with bipolar disorder. Because of the controversy about whether childhood bipolar disorder is similar to adulthood bipolar disorder [20, 21], we excluded studies in which the mean age of participants was < 12 years. We included only primary studies (i.e. no meta-analyses or reviews) published in peer-reviewed, English-language journals.

Search strategy

We searched PubMed and PsycINFO from inception until October 2022. Our search strategy (see Supplementary Material for the search terms) aimed to identify manuscripts meeting eligibility criteria described above.

Study selection and data extraction

After exclusion of duplicates, titles and abstracts were independently reviewed by two raters and excluded if they clearly did not satisfy our inclusion criteria. Disagreements were resolved by discussion with a third rater. In case of doubt, the report was included in the full text review. We retrieved the full text of all papers that passed title-abstract review. Full text review and data extraction was performed by one rater using a data extraction form specific to one of the five study types outlined above, which was also used in our previous systematic review [17].

Quality rating

We assessed the methodological quality of molecular-genetic and family studies based on two different lists of quality criteria (Supplementary Material). Quality ratings were performed by one rater, and discussed with a second rater if needed. Power for each analysis was based on analysis type and whether the phenotype measure, and/or measure of genetic difference was continuous, categorical, or dichotomous (Supplementary Tables 7/8). Based on methodologic rigor and power, we rated each analysis as "high", "moderate", "low" or "very low" in quality.

Data synthesis

We grouped similar phenotypes into larger categories and synthesized the results by phenotype category (and in case of a sufficiently large number of analyses, by specific phenotype), focusing on whether the evidence supported an effect in a uniform direction. From each relevant statistical test, we extracted the effect size, direction of effect, and P-values. If the same phenotype was analyzed multiple times in the same or in overlapping samples in different papers, we selected the largest available sample only. We examined the available evidence for each of the five study types separately. Due to the heterogeneity in study methods and often limited reporting of results (e.g. missing effect sizes and imprecise P-values), we could not perform a meta-analysis. We assessed the overall evidence per phenotype as strong, moderate, or weak, based on the number of studies, their quality, power, and the consistency of the findings. Because of the highly different designs of molecular genetic studies and family based studies, we used different rules for aggregating the evidence of both types of studies, which are described in the Supplementary Material.

RESULTS

Search results and study selection

We identified 2693 unique published records through electronic database searches (Fig. 1). After title/abstract screening, 2298 records were excluded for not meeting our inclusion criteria. We included 395 records for full-text review, of which four could not be retrieved. Hence, we assessed the full texts of 391 reports. After full text review, 253 reports were excluded mostly because of having no relevant genetic analysis or no original data. This resulted in a total of 142 reports included in this systematic review. These 142 reports often contained multiple analyses (e.g., investigating multiple phenotypes), and sometimes different types of analyses (e.g., PRS-based analyses and other molecular genetic analysis, e.g., [5]), resulting in a total of 445 relevant analyses. For PRS studies, we distinguished between analyses using bipolar disorder, schizophrenia, or major depressive disorder PRSs (PRS-BD, PRS-SCZ and PRS-MDD, resp.), or any other PRS (counting the latter as a single analysis even if multiple other PRSs were examined). Most analyses were based on studies of family aggregation (71 articles including 199 analyses), followed by PRS studies (37 articles including 167 analyses). In addition, we identified 18 articles with 47 affected-pair analyses, 8 articles with 16 genetic modelling analyses, and 15 articles with 16 other molecular-genetic analyses (Table 1). The number of each analysis type contained in each article and full references are provided in Supplementary Table 1.

Summary of the evidence

We categorized the most frequently studied phenotypes into 14 categories (Table 1). Most analyses were performed on comorbidity (58 analyses), course of illness (57 analyses), onset (56 analyses), and affective symptoms (52 analyses). Below we describe the evidence by study type, starting with the studies using molecular genetic data and then the studies with a family design. For a detailed description and summary of the evidence by study type we refer to the Supplementary Material.

Evidence from PRS-based studies. A total of 167 analyses investigated whether certain phenotypes in subjects with bipolar disorder indicated differences in PRS (Supplementary Table 2). While we were primarily interested in the association with bipolar PRS, here we also summarize moderate to strong evidence for other PRSs, such as schizophrenia (SCZ), major depressive disorder (MDD), or sleep related PRSs.

We found strong evidence that bipolar I, bipolar II, and schizoaffective disorder were differentially associated with several PRS. Bipolar I was more strongly associated with PRS-SCZ than bipolar II, whereas bipolar II was more strongly associated with PRS-MDD than bipolar I. One study showed that the higher association between PRS-SCZ and bipolar I could possibly be explained by the presence of psychotic symptoms in bipolar I [10]; this was not true for the stronger association between PRS-MDD and bipolar II [10]. There was also moderate evidence that PRS for bipolar disorder (PRS-BIP) was higher in bipolar I than in bipolar II, whereas bipolar II was associated with higher PRS-insomnia and lower PRS-sleep duration. Schizoaffective disorder, bipolar type (SAB) was more highly associated with PRS-SCZ than bipolar I and II, whereas bipolar I and II were more highly associated with PRS-MDD than SAB.

Other strong evidence found that genetic risk factors predicted psychotic symptoms in patients with bipolar disorder. Bipolar subjects with psychotic symptoms had a higher PRS-SCZ (strong evidence) and PRS-BIP (moderate evidence) than subjects without psychotic symptoms. There was also moderate to strong evidence that mood-incongruent psychotic features in bipolar disorder were particularly associated with PRS-SCZ.

Furthermore, we found moderate evidence that PRS-SCZ and PRS-BIP were associated with more manic symptoms and PRS-MDD with fewer manic symptoms. There was also moderate evidence that suicide attempts may be indexing a higher PRS-MDD in subjects with bipolar disorder.

We found weak evidence that subjects with an earlier age at onset, lower cognitive performance, comorbid anxiety or substance use disorders, course of illness (i.e., lower number of episodes, less rapid cycling, more hospitalizations), and poor lithium response had a higher PRS-BIP, PRS-SCZ, and/or PRS-MDD (Supplementary Material). However, these phenotypes were investigated too infrequently and/or lacking high quality studies to draw stronger conclusions.

Evidence from other molecular-genetic studies

A total of 16 studies in 2 independent cohorts/samples (8 studies used the PGC2/3 samples, 6 studies used subsamples of the PGC2/3, 2 studies used the independent ConLiGen sample) were performed (Supplementary Table 3).

Nine studies (eight high quality) investigated genetic differences between subtypes of bipolar disorder, mainly bipolar I, bipolar II, and schizoaffective disorder in PGC2/3 or subsamples. These studies provide strong evidence for a different genetic architecture of these subtypes. First, there is strong evidence that SNP-h2 of bipolar I is higher than SNP-h2 of bipolar II. The largest study ($N \sim 32{,}000$, PGC3) [5] also showed that the genetic correlation between bipolar I and bipolar II is high, but significantly lower than 1 ($r_g = 0.85$), and – in line with the PRS-based findings in PGC2 [10] – that the genetic correlation between schizophrenia and bipolar I was higher than the genetic correlation between schizophrenia and bipolar II, whereas the genetic correlation between bipolar II and MDD was higher than that between bipolar I and MDD. A study in the same PGC3 sample showed that bipolar I was also more genetically correlated with schizoaffective disorder than bipolar II.

Other strong evidence was found in one very large high-quality study for a similar SNP-h^2 (~0.19) in both men and women, indicating that quantitatively the magnitude of genetic risk for bipolar disorder was similar across sexes. However, the genetic correlation between men and women was significantly less than 1 (PGC2, $N = 18{,}958$) [22], suggesting qualitative differences in the genetic risk in men and women.

Furthermore, there was moderate evidence that psychotic symptoms in bipolar I were *not* associated with CNV burden based on one large high-quality study [23].

There was weak evidence for the association between earlier age at onset and CNV deletions or number of CNVs. We found inconsistent evidence for the genetic relevance of good lithium

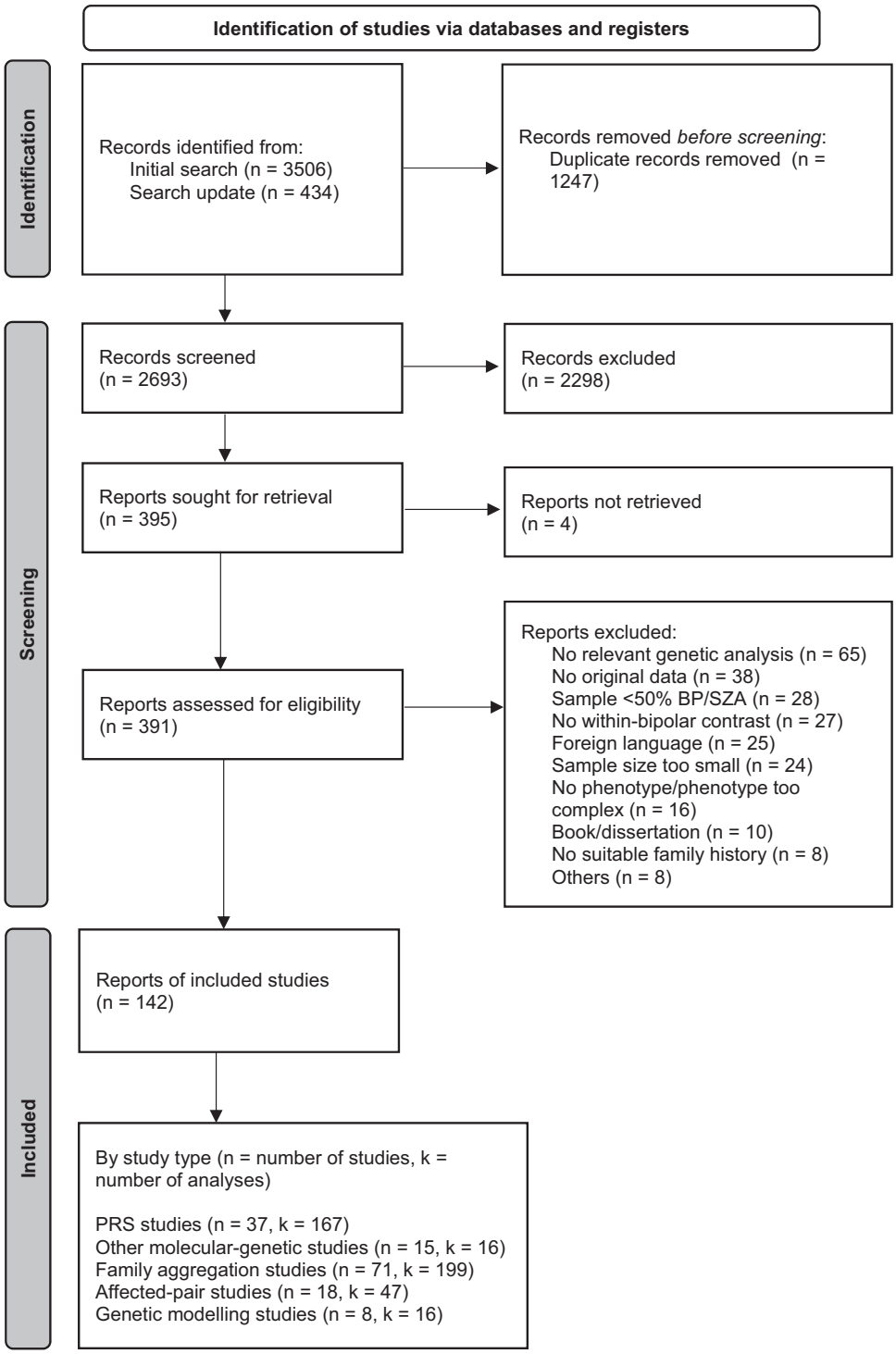

Fig. 1 Flow diagram of the systematic review. Diagram of the number of records identified through search, screened based on title and abstract, assessed for eligibility based on the full text, and finally included in the systematic review.

response, and weak evidence for ethnicity (significant genetic correlation between European and Han Chinese cases) (Supplementary Material). The evidence was weak based on the number and quality of studies, and they are described in the Supplementary Material.

Evidence from family-based studies

Most studies ($n = 71$, $k = 199$) used a family-based design to investigate the association between a certain clinical characteristic in a proband with bipolar disorder and the number/presence of affected family members (Table 2, Supplementary Table 4).

The studies differed considerably in size and quality. There were few high-quality family-based papers with the majority graded as moderate or lower quality. This was related to the fact that many family-based studies were underpowered or investigated a family history of affective disorders or psychiatric disorders in general (instead of family history of bipolar disorder specifically) reducing the specificity of the findings.

Table 1. Number of each analysis type by phenotype category.

Phenotype Category	Number of analyses (Number of papers/number of independent samples)					
	PRS	Other molecular genetic	Familial aggregation	Affected pair	Genetic modelling	Total number of analyses
Affective symptoms	16 (4/3)	0	20 (10/9)	12 (4/3)	4 (2/1)	52
Cognition	5 (2/3)	0	5 (4/4)	0	5 (1/1)	15
Comorbidity	19 (7/2)	0	33 (17/14)	6 (5/1)	0	58
Course	27 (6/3)	0	24 (15/12)	6 (6/3)	0	57
Diagnosis/subtype	19 (12/4)	9 (9/1)	12 (12/10)	2 (2/2)	2 (2/2)	44
Environmental risk factors	2 (2/2)	0	8 (7/6)	0	0	10
Family history	6 (4/2)	0	0	0	0	6
Functioning	0	0	7 (5/5)	0	0	7
Gender	2 (2/2)	1 (1/1)	8 (8/8)	2 (2/2)	1 (1/1)	14
Medication responsiveness	7 (4/1)	2 (2/1)	10 (9/8)	0	0	19
Onset (age/mode)	15 (8/3)	2 (2/1)	32 (30/27)	6 (6/4)	1 (1/1)	56
Other	2 (2/2)	1 (1/1)	15 (10/10)	2 (1/1)	2 (2/2)	22
Psychosis	27 (13/2)	1 (1/1)	15 (14/13)	7 (6/3)	1 (1/1)	51
Suicidality	20 (9/5)	0	10 (10/10)	4 (4/2)	0	34
Total number of analyses	167	16	199	47	16	445

By far the most studies (30 studies in 27 distinct samples in total) investigated age at onset as an indicator of familial risk. Although there were 13 analyses in which there was no association between age at onset and familial risk of bipolar disorder, the other analyses including the largest studies consistently showed an association between earlier age at onset and increased familial risk of bipolar disorder (except for one very low-quality study showing the reverse).

There was moderate evidence from 12 studies in 10 distinct samples that bipolar I was specifically associated with bipolar I in relatives, while bipolar II may be specifically associated with bipolar II in relatives. In contrast to the molecular genetic studies, there was little evidence that bipolar subtypes were associated with increased familial risk of bipolar disorder in general.

For some phenotypes, we found a reasonable number of distinct analyses (i.e., 8–13), but the overall evidence for these phenotypes was rated as weak because there were an insufficient number of studies in general or insufficient number of high-quality studies specifically. These studies found weak evidence that psychotic symptoms, comorbid anxiety disorders, episode frequency, medication responsiveness, and suicidality in subjects with bipolar disorder were associated with increased familial risk of bipolar disorder.

There was also weak evidence that sex (male/female) was *not* associated with increased familial risk of bipolar disorder. For the other results we refer to the summary in the Supplementary Material.

Evidence from affected relative pair studies

A total of 18 studies describing 47 analyses investigated whether certain phenotypes were correlated within a pair of relatives (mostly siblings) affected with bipolar disorder (Table 3, Supplementary Table 5). These phenotypes could index genetic factors ('modifier genes') that may alter the clinical presentation of bipolar illness, without necessarily increasing the risk for bipolar illness itself [16]. Taken together, these studies provided weak evidence for the concordance of psychosis, mania-related symptoms, and age of onset among relatives affected with bipolar disorder. There was also weak evidence for the familiality of suicidality, as well as weak evidence that pairs of affected relatives were no more likely than chance to be concordant for sex. For other phenotypes the evidence was either very weak (e.g., anxiety disorders, rapid mood switching/cycling) or inconsistent (e.g., depressive symptoms, subtype) due to few studies or low quality studies. As expected, there was no evidence of negatively correlated phenotypes among pairs of relatives. This would only occur in the unlikely situation where the presence of a trait in one relative predicts the absence of the same trait in the other relative.

Evidence from genetic modelling studies

A total of 8 studies used genetic modelling methods to investigate genetic relevance of phenotypic heterogeneity among subjects with bipolar disorder (Supplementary Table 6, Supplementary Material). Taken together, these studies provided very weak evidence from a single sample for the heritability of depressive symptoms, irritable mania, and age of onset. Additionally, there was very weak evidence from a single sample that the genetic liabilities to several cognition-related phenotypes and bipolar disorder are associated. There was insufficient evidence for heritability of psychosis, sleep characteristics, or a difference in heritability based on sex or bipolar subtype.

Overall summary of results

Table 4 provides an overview of the evidence for the genetic relevance of specific phenotypes from all study types.

Table 2. Findings from family aggregation studies.

Findings from family aggregation studies: total (high quality)						
Phenotype category	**Positive association**				**No association**	**Negative association**
	Significant	**Marginal**	**Trend**	**Total**		
Affective symptoms	1 (0)	2 (0)	0 (0)	3 (0)	5 (1)	1 (0)
Depressive symptoms	1 (0)	1 (0)	0 (0)	2 (0)	3 (1)	0 (0)
Manic symptoms	0 (0)	2 (0)	0 (0)	2 (0)	2 (0)	0 (0)
Mixed symptoms	2 (0)	0 (0)	0 (0)	2 (0)	0 (0)	1 (0)
Other (e.g. affective balance)	1 (0)	0 (0)	0 (0)	1 (0)	2 (0)	0 (0)
Cognition	0 (0)	1 (0)	0 (0)	1 (0)	3 (1)	0 (0)
Comorbidity	2 (0)	2 (0)	0 (0)	4 (0)	9 (2)	1 (0)
Anxiety	2 (0)	1 (0)	0 (0)	3 (0)	7 (1)	0 (0)
Other	1 (0)	1 (0)	0 (0)	2 (0)	4 (0)	0 (0)
Substance use	0 (0)	2 (0)	0 (0)	2 (0)	7 (2)	1 (0)
Course	2 (1)	3 (0)	1 (0)	6 (1)	6 (1)	0 (0)
Rapid cycling	1 (0)	0 (0)	0 (0)	1 (0)	4 (1)	0 (0)
Episode frequency	2 (1)	3 (0)	1 (0)	6 (1)	3 (0)	0 (0)
Hospitalization	1 (0)	2 (0)	0 (0)	3 (0)	1 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)
Diagnosis/subtype	3 (3)	1 (0)	0 (0)	4 (3)	6 (2)	0 (0)
Environmental factors	1 (0)	0 (0)	0 (0)	1 (0)	5 (0)	0 (0)
Functioning	1 (0)	1 (0)	0 (0)	2 (0)	3 (1)	0 (0)
Sex (male/female)	0 (0)	0 (0)	0 (0)	0 (0)	8 (2)	0 (0)
Medication responsiveness	1 (0)	4 (0)	1 (0)	6 (0)	2 (1)	0 (0)
Age at onset	7 (3)	3 (1)	3 (0)	13 (4)	13 (2)	1 (0)
Psychosis	1 (1)	1 (0)	2 (0)	4 (1)	8 (3)	1 (0)
Suicidality	2 (0)	1 (0)	0 (0)	3 (0)	7 (1)	0 (0)

Table 3. Findings from affected relative pair studies.

Findings from affected pair studies: total (high quality)					
Phenotype category	**Positive association**				**No association**
	Significant	**Marginal**	**Trend**	**Total**	
Affective symptoms	1 (0)	2 (1)	0 (0)	3 (1)	0 (0)
Affective balance	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)
Depressive symptoms	2 (1)	0 (0)	0 (0)	2 (1)	1 (1)
Manic symptoms	1 (0)	2 (1)	0 (0)	3 (1)	0 (0)
Comorbidity	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Anxiety	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Substance use	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Course of illness	2 (0)	1 (1)	0 (0)	3 (1)	0 (0)
Episode frequency	1 (0)	1 (1)	0 (0)	2 (1)	0 (0)
Perinatal episodes	1 (0)	1 (0)	0 (0)	2 (0)	0 (0)
Rapid cycling/switching	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Diagnosis/subtype	1 (0)	0 (0)	0 (0)	1 (0)	1 (0)
Sex (male/female)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)
Onset	3 (1)	0 (0)	0 (0)	3 (1)	1 (0)
Age at onset	3 (1)	0 (0)	0 (0)	3 (1)	1 (0)
Polarity at onset	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)
Psychosis	3 (1)	0 (0)	0 (0)	3 (1)	0 (0)
Any psychosis	3 (1)	0 (0)	0 (0)	3 (1)	0 (0)
Mood incongruence	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Suicidality	2 (0)	0 (0)	0 (0)	2 (0)	0 (0)

Table 4. Overall summary of the evidence.

	Phenotype	Level of evidence	Type of studies	Specification
Phenotypes that index genetic risk for bipolar disorder	Lower age at onset	Strong	FA	
	Bipolar I vs Bipolar II	Strong	Other mol.gen.	SNP-h2 bipolar I > bipolar II
		Moderate	PRS	PRS-BIP bipolar I > bipolar II
	Psychotic symptoms	Moderate	PRS	
	Manic symptoms	Moderate	PRS	
Phenotypes that index other genetic differences	Bipolar I vs Bipolar II	Strong	Other mol.gen.	rg < 1
		Strong	Other mol.gen.	rg bipolar I - SCZ > rg bipolar II - SCZ
		Strong	Other mol.gen.	rg bipolar II - MDD > rg bipolar I - MDD
		Strong	Other mol.gen.	rg bipolar I - SZA > rg bipolar II - SZA
		Strong	Other mol.gen.	rg bipolar II - daytime sleepiness > rg bipolar I - daytime sleepiness
		Moderate	PRS	PRS-SCZ bipolar I > bipolar II
		Moderate	PRS	PRS-MDD bipolar II > bipolar I
		Moderate	PRS	PRS-insomnia bipolar II > bipolar I
		Moderate	FA	Bipolar I is related to bipolar I in family members, and bipolar II to bipolar II
	Schizoaffective disorder	Moderate	PRS	PRS-SCZ SZA > PRS-SCZ in bipolar I/II
	Psychotic symptoms	Strong	PRS	higher PRS-SCZ
	Manic symptoms	Moderate	PRS	higher PRS-SCZ, lower PRS-MDD
	Suicide attempts	Moderate	PRS	higher PRS-MDD
	Sex (male/female)	Strong	Other mol.gen.	rg < 1
Phenotypes that do NOT index genetic risk for bipolar disorder	Sex (male/female)	Strong	Other mol.gen.	SNP-h2 identical
	Psychotic symptoms	Moderate	Other mol.gen.	*no* difference in CNV burden

BIP Bipolar disorder, *CNV* Copy number variants, *FA* Family aggregation studies, *MDD* Major depressive disorder, *Other mol.gen.* Other molecular genetic studies, *PRS* Polygenetic risk score, *rg* Genetic correlation, *SNP-h2* SNP-heritability, *SCZ* Schizophrenia, *SZA* Schizoaffective disorder.
This table summarizes the phenotypes for which moderate to strong evidence of their genetic relevance in bipolar disorder exists.

DISCUSSION

Summary of main findings

We systematically reviewed, for the first time, all molecular genetic, family, and twin studies investigating the genetic relevance of specific clinical characteristics of bipolar disorder. We summarized the evidence from 142 articles including 445 relevant analyses, and found moderate to strong evidence that lower age at onset, bipolar I (in comparison with bipolar II), psychotic symptoms, and manic symptoms index a higher genetic risk of bipolar disorder. All these phenotypes except for age at onset were also associated with other genetic differences, such as that bipolar I is more genetically correlated with schizophrenia, and bipolar II with major depressive disorder. Lastly, we found strong evidence that sex does not have an overall quantitative effect on genetic risk of bipolar disorder but appears to reflect some qualitative genetic differences.

Relation with previous literature

No previous systematic reviews exist that examine the genetic relevance of clinical characteristics in bipolar disorder in both family and molecular-genetic studies. Two previous reviews suggested that an early age at onset, psychotic symptoms, and response to lithium could index a higher genetic risk in bipolar disorder [13, 14], but these reviews were not systematic and did not include the latest studies including large-scale molecular genetic studies. A recent systematic review specifically examined correlation of phenotypes in affected relatives [15]; while this review identified statistically significant (though limited) evidence for several phenotypes including age of onset, bipolar type, and lithium response, we concluded (largely on the basis of the same set of studies) that there was at best only weak evidence from affected-relative-pair studies for any phenotype, as no phenotype was supported by more than three studies. Two other recent systematic reviews investigated phenotypes associated with PRS-BD, PRS-MDD, and PRS-SCZ, but not specifically in subjects with bipolar disorder [24, 25]. The most comparable study to date is the review we recently performed on clinical characteristics indexing genetic risk for schizophrenia [17].

We observed several similarities in the results of our reviews. First, lower age at onset indexed a higher genetic risk for both disorders. This was expected as it is a common finding in a range of psychiatric and medical disorders [26–29]. Second, age at onset, psychotic symptoms, and manic symptoms may index genes that modify the clinical presentation of both disorders, although the overall evidence for these phenotypes was weaker in bipolar disorder than in schizophrenia due to a lower number of affected

pair studies in bipolar disorder (weak versus moderate/strong evidence based on 47 versus 195 analyses). Although the substantial genetic overlap between both disorders has been demonstrated before (r_g=0.68 PGC3) [5, 30, 31], our study suggests that there is also overlap in the clinical characteristics that index increased genetic risk in both disorders.

However, there were also differences between the two types of disorders. Among patients with bipolar disorder, the presence of psychotic symptoms (delusions, hallucinations) appears to be related to genetic loading for bipolar disorder and also to genetic loading for schizophrenia. However, there was insufficient evidence to say whether negative symptoms in patients with bipolar disorder are associated with genetic factors, because most questionnaires assessed positive symptoms more extensively than negative symptoms in bipolar disorder (e.g., [32–34]). In schizophrenia by contrast, there was strong evidence that the severity of negative symptoms indexes high genetic loading for schizophrenia [17]. However, the severity of positive symptoms (delusions, hallucinations) did not appear to be associated with genetic loading for schizophrenia. We speculate that positive psychotic symptoms may be better able to differentiate in patients with bipolar disorder (who may or may not experience any positive psychotic symptoms) than in patients with schizophrenia (who almost invariably experience positive psychotic symptoms).

The most striking difference concerned sex. We found strong evidence that sex does *not* index a difference in overall genetic risk for bipolar disorder, although the genetic correlation for men and women was significantly smaller than 1, suggesting possible qualitative genetic differences. In our previous review, on the other hand, we found moderate evidence that female sex was associated with a higher genetic risk in schizophrenia [17]. This suggests relevant genetic differences across bipolar disorder and schizophrenia, which may be reflected in their differences in epidemiology. In bipolar disorder, the prevalence rates and age at onset in men and women are similar [35, 36], whereas in schizophrenia, the prevalence is higher in men and their age at onset lower than in women [37–39]. This pattern of findings is consistent with a possible female protective effect against schizophrenia but not bipolar disorder.

In our previous review, we did not find much evidence for the genetic relevance of diagnostic subtypes of schizophrenia (e.g. paranoid schizophrenia). This contrasts with this review, as some of the strongest findings in this review concerned the distinction between the diagnostic subtypes bipolar I and II. The distinction between bipolar I and II was first described in the DSM-IV in 1994 [40, 41], but the distinction between classical mania and hypomania –one of the main differences between bipolar I and II– was already described in 1881 by Emanuel Mendel, repeatedly cited by Kraepelin [42, 43]. The findings of our review confirm the genetic relevance of these subtypes (and related, also the relevance of the severity of manic symptoms) as indices of genetic risk of bipolar disorder. Our results also support the idea that in terms of genetics, bipolar I is more closely related to schizophrenia, while bipolar II is more closely related to major depressive disorder. However, there was also some evidence to suggest that the higher association between bipolar I and PRS-SCZ could be explained by the presence of psychotic symptoms in bipolar I, more so than in bipolar II. This means that psychotic symptoms in bipolar disorder could be a more relevant index of genetic risk of schizophrenia than the presence of mania vs. hypomania.

Although similar systematic reviews have not been performed for other disorders, it is likely that at least age at onset [26, 29, 44], sex [44, 45], and the presence of psychotic symptoms [46] may be relevant phenotypes for other psychiatric disorders as well.

Limitations

The results of this systematic review should be interpreted considering several limitations. First, despite having performed an electronic database search with a broad set of search terms to cover the variety of terms used to describe the relevant studies, we may have missed studies that used different terminology. Furthermore, many molecular genetic studies are currently being performed and an update of this review would be desirable in the future.

Second, we could not perform a meta-analysis to quantify the overall strength of association between the phenotype and familial/genetic risk of bipolar disorder because of heterogeneity of study methods among the included reports.

Third, for many phenotypes there were insufficient numbers of studies, and/or high-quality studies, to draw conclusions about the relevance of the phenotype for indexing genetic risk. In general, the number of analyses performed was lower for bipolar disorder than for schizophrenia (400 vs 800 analyses) [17]. This resulted in weak evidence for several potentially relevant phenotypes, including for medication responsiveness, course of illness and comorbidity. Future studies are needed to evaluate the associations between these phenotypes and genetic factors.

Fourth, many familial aggregation studies assessed the relation between a phenotype and a family history of psychiatric disorders or mood disorders in general, instead of a family history of bipolar disorder specifically. This means that a positive association between a phenotype in the proband and a positive family history could mostly be driven by major depressive disorder, for instance, given the much higher prevalence of unipolar mood disorder than of bipolar disorder. We chose to downgrade the quality of these studies, as the nature of the genetic risk is unclear, which is one reason why there was a low number of high-quality family studies. There were a few phenotypes (e.g., psychosis) that may also have had at least moderate evidence from family studies if we had not made this choice.

Fifth, roughly half of the included analyses used a familial aggregation design to study the relevance of a specific phenotype for familial risk of bipolar or other psychiatric disorders. The associations found in these studies cannot distinguish between genetic effects or shared environmental effects. However, it is likely that most of the found associations in these studies can be explained by genetic factors as there is little evidence from twin studies that shared family environment plays a major role in familial transmission of bipolar disorder [13].

CONCLUSIONS

Our systematic review identified age at onset, subtypes of bipolar disorder (especially bipolar I and II), manic symptoms, and psychotic symptoms as clinical characteristics with good evidence that they index genetic differences in bipolar disorder. Assessing these features in samples used for large-scale molecular genetic studies will likely increase power to identify novel genetic variants and more specific biological pathways of bipolar disorder.

Although increasing sample sizes in genetic studies of bipolar disorder are expected to lead to more genetic findings [5], assessing diagnoses alone will most likely not be sufficient to understand the etiology of heterogeneous disorders such as bipolar disorder [8]. The set of clinical characteristics indexing relevant genetic differences in bipolar disorder that we identified in this review are good starting points for further genetic analyses in bipolar disorder. Our results also demonstrate the importance of future studies to investigate the genetic relevance of other phenotypic features in bipolar disorder.

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AUTHOR CONTRIBUTIONS

HL, YV, JT, and KK contributed to the conception and design of the study. HL, YV, JT, LT, and CD contributed to the literature search and data extraction. HL, YV, and JT contributed to the analysis of the results. HL wrote the first draft of the manuscript, which was critically revised by all other authors. All authors approved the final draft of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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