Review Article

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Insights into the genomics of affective disorders

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Abstract: Affective disorders, or mood disorders, are a group of neuropsychiatric illnesses that are characterized by a disturbance of mood or affect. Most genetic research in this field to date has focused on bipolar disorder and major depression. Symptoms of major depression include a depressed mood, reduced energy, and a loss of interest and enjoyment. Bipolar disorder is characterized by the occurrence of (hypo)manic episodes, which generally alternate with periods of depression. Formal and molecular genetic studies have demonstrated that affective disorders are multifactorial diseases, in which both genetic and environmental factors contribute to disease development. Twin and family studies have generated heritability estimates of 58–85 % for bipolar disorder and 40 % for major depression.

Large genome-wide association studies have provided important insights into the genetics of affective disorders via the identification of a number of common genetic risk factors. Based on these studies, the estimated overall contribution of common variants to the phenotypic variability (single-nucleotide polymorphism [SNP]-based heritability) is 17–23 % for bipolar disorder and 9 % for major depression. Bioinformatic analyses suggest that the associated loci and implicated genes converge into specific pathways, including calcium signaling. Research suggests that rare copy number variants make a lower contribution to the development of affective disorders than to other psychiatric diseases, such as schizophrenia or the autism spectrum disorders, which would be compatible with their less pronounced negative impact on reproduction. However, the identification of rare sequence variants remains in its infancy, as available next-generation sequencing studies have been conducted in limited samples. Future research strategies will include the enlargement of genomic data sets via innovative recruitment strategies; functional analyses of known associated loci; and the development of new, etiologically based disease models. Researchers hope that deeper insights into the biological causes of affective disorders will eventually lead to improved diagnostics and disease prediction, as well as to the development of new preventative, diagnostic, and therapeutic strategies. Pharmacogenetics and the application of polygenic risk scores represent promising initial approaches to the future translation of genomic findings into psychiatric clinical practice.

Keywords: affective disorders, mood disorders, bipolar disorder, major depressive disorder, genomics

Introduction

Affective disorders, or mood disorders, represent a major global health concern due to their associated morbidity, mortality, and socioeconomic costs for affected individuals and society [1, 2]. Affective disorders are a group of neuropsychiatric illnesses, whose main symptom is a disturbance of mood or affect [3]. Affected individuals experience single or recurrent episodes of mood disturbance, ranging from severe depression to mania. In between episodes, the mood state is euthymic, i. e., the patient does not fulfill the diagnostic criteria for either mania or depression. The diagnosis of an affective disorder relies on the clinical history and a mental state examination. While laboratory tests are conducted to exclude other medical conditions, no laboratory test is yet available to confirm or exclude a suspected affective disorder diagnosis. Furthermore, therapy is symptomatic and often suboptimal, and no major therapeutic breakthroughs have been achieved for several decades. One important reason for this is our limited knowledge of the underlying molecular biology. Therefore, a crucial prerequisite for the development of new preventative, diagnostic, and therapeutic approaches for affective disorders is an understanding of

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their biological causes. Since family history is a major risk factor, genetic approaches are of key importance. These were initiated more than 30 years ago, with limited initial success. As is true for many other common diseases, major obstacles within affective disorder research have been a lack of: (i) knowledge concerning the human genome and inter-individual genomic variation; and (ii) appropriate molecular genetic technologies (e. g., genome-wide genotyping). Since the completion of the human reference genome sequence, however, knowledge and technologies have undergone rapid advancement. Over the past decade, molecular genetic studies have generated important insights into the underlying biology of the two most widely investigated affective disorders within psychiatric genetics to date: bipolar disorder and major depression. The present review summarizes the key findings of this research.

Clinical characteristics of bipolar disorder and major depression

Current classification systems (International Classification of Diseases [ICD] and Diagnostic and Statistical Manual of the American Psychiatric Association [DSM]) categorize affective disorders on the basis of the constellation, duration, and severity of symptoms (e. g., [3, 4]).

Major depression is characterized by single or recurrent episodes of depression. The diagnostic criteria for a depressive episode include a depressed mood, reduced energy, and a loss of interest and enjoyment [5]. Additional symptoms comprise reduced concentration, disturbed sleep behavior, and suicidal thoughts [5, 6]. The diagnosis of "major depressive disorder" is based on structured diagnostic criteria with a minimum symptom duration of 2 weeks [4, 5]. However, as some studies include "case" definitions of depression that may not fulfill the diagnostic criteria for major depressive disorder (e. g., individuals with self-reported depression), the term ''major depression'' is used to reflect the inclusion of differently phenotyped samples [5].

Bipolar disorder is characterized by the occurrence of (hypo)manic episodes, which typically alternate with episodes of depression [7]. Manic episodes are periods of elevated or irritable mood lasting at least 1 week [4]. In hypomanic phases the symptoms are less pronounced and not severe enough to cause significant functional impairment [4]. At the phenotypic level, two major clinical subtypes are distinguishable: (i) bipolar disorder type I (BD1), which is typically characterized by a history of recurring manic and depressive episodes; and (ii) bipolar disorder type II (BD2), whose diagnosis is based on the lifetime occurrence of at least one depressive and one hypomanic episode [8]. In patients presenting with clinical features of both bipolar disorder and schizophrenia, a diagnosis of schizoaffective disorder bipolar type (SAB) is assigned [8].

Affective disorders have a high prevalence within the general population. The estimated lifetime prevalence of bipolar disorder is around 1–2 % [9]. In the majority of studies, no sex differences in disease prevalence have been observed [10]. The lifetime prevalence of major depressive episodes is around 11–15 %, with a 2-fold higher rate observed in women compared with men [11].

Formal genetic and early candidate gene studies in bipolar disorder and major depression

Based on the results of formal and molecular genetic studies (see also the following sections), the current consensus among researchers is that affective disorders are multifactorial diseases, i. e., they are disorders in which both genetic and environmental factors contribute to disease development [7, 12]. Twin and family studies indicate that the contribution of genetic factors to bipolar disorder is pronounced, with an estimated heritability of between 58–85 % having been reported [13, 14]. For major depression, the estimated heritability is around 40 %, and research suggests that the etiological role of environmental factors is higher than is the case for bipolar disorder [15]. The hypothesis that genetic factors contribute to the development of bipolar disorder and major depression is further supported by the fact that genetic relatedness (i. e., similarity) is a major, established risk factor. The first-degree relatives of bipolar disorder patients show a 5.8–7.9-fold increase in the risk of developing the disorder [14], while the first-degree relatives of patients with major depression show an approximately 2- to 3-fold increase in the risk for major depression [15, 16]. The observation that disease risk decreases in individuals who are more distantly related to a patient with an affective disorder (e. g., [14]) provides additional support for the involvement of genetic factors.

As with other multifactorial diseases and phenotypes, formal genetic evidence for the involvement of genetic factors in affective disorders does not provide insights concerning the underlying genetic architecture. Early molecular genetic studies focused on candidate genes and were

conducted under the assumption of the existence of common genetic risk factors with strong genetic effect sizes (i. e., penetrance). This incorrect assumption led to inconsistent results, which generated major frustration among researchers, patients, and the wider public alike. However, a more realistic picture of the nature of the genetic factors that underlie psychiatric disease has been obtained since the introduction of the genome-wide association study (GWAS) approach, which allows the efficient and genome-wide investigation of common genetic variants with small effects [17].

Molecular genetic findings in bipolar disorder

To date, the most comprehensive and systematic insights into the molecular genetics of bipolar disorder have been obtained through GWAS. For bipolar disorder, the largest GWAS to date was conducted by the Psychiatric Genomics Consortium (PGC), and included data from around 30,000 patients and 169,000 controls. This study identified a total of 30 genome-wide significant loci [8]. The authors demonstrated that overall, common risk variants accounted for approximately 17–23 % of the phenotypic variance of bipolar disorder (so-called single-nucleotide polymorphism [SNP]-based heritability) [8]. Another highly interesting observation is the existence of a substantial genetic overlap between bipolar disorder and schizophrenia. Eight of the 30 loci identified for bipolar disorder had shown a previous association with schizophrenia [18, 19]. The investigation of genetic correlations between bipolar disorder and other diseases/phenotypes has revealed significant positive genetic correlations with other psychiatric disorders, namely, major depression, anorexia nervosa, and autism spectrum disorder, as well as measures of educational attainment [8]. These findings suggest that many of the identified risk variants confer susceptibility to multiple brain phenotypes, i. e., they have pleiotropic effects.

GWAS data facilitate the generation of biological information beyond the level of individual risk variants. In particular, biological pathway analyses recognize association patterns across different genomic loci that converge into specific biological pathways [20]. In bipolar disorder research, significant enrichments have been described, among others, for the regulation of insulin secretion and retrograde endocannabinoid signaling [8]; neurodevelopmental processes [21]; histone H3-K4 methylation [22]; and calcium signaling [23].

The detailed analysis of GWAS data has revealed differences in the genetic architecture of the clinical subtypes BD1 and BD2, whereby: (i) BD1 showed a significantly higher SNP-based heritability than BD2 [24]; and (ii) BD1 showed a stronger genetic correlation with schizophrenia, whereas BD2 was genetically more related to major depression [8]. These results suggest that the clinical bipolar disorder subtypes belong to a spectrum of genetically correlated neuropsychiatric disorders [8].

The generated GWAS data can also be used to calculate polygenic risk scores (PRS, see also the article by Andlauer et al. in the present issue), which allow the assessment of individual genetic risk profiles based on imputed genotype data [25]. In addition, PRS can be used to help explain the aggregation of disease within families. For example, a recent study calculated PRS in 33 multiply affected bipolar disorder families and an independent, bipolar disorder case/control cohort from Spain [26]. Interestingly, both familial bipolar disorder patients and unaffected family members had higher PRS for bipolar disorder, major depression, and schizophrenia than the independent controls [26]. In addition, familial bipolar disorder patients had significantly higher PRS for bipolar disorder than either unaffected family members or unrelated patients with bipolar disorder. These findings suggest that while multiply affected families have an increased, nonspecific baseline risk for several psychiatric disorders, the development of bipolar disorder might be attributable to a high burden of common variants that confer a specific risk for bipolar disorder [26]. However, given that the generated PRS explained only a part of the estimated genetic contribution, the authors assumed that rare genetic variants might also contribute to disease etiology [26].

An important, and often functionally relevant, class of rare variants is that of the copy number variants (CNVs). Research into mental disorders with a strong neurodevelopmental component, such as schizophrenia and the autism spectrum disorders, has identified several rare CNVs with relatively strong genetic effects (e. g., [27]). Green and colleagues investigated the frequency of CNVs at 15 genomic loci that had been implicated in schizophrenia in a bipolar disorder case/control cohort [28]. After correction for multiple testing, only duplications at 16p11.2 were significantly associated with bipolar disorder [28]. A recent study by Charney and colleagues investigated rare large CNVs in a sample of around 6,400 bipolar disorder patients and 8,700 controls [29]. The authors found that in the overall sample, the CNV burden did not differ between bipolar disorder patients and controls. However, patients with SAB had an increased CNV burden compared with controls and patients with BD1 or BD2 [29]. Together with

the results of previous studies (e. g., [30]), these findings suggest that: (i) CNVs might contribute less to the development of bipolar disorder than to other psychiatric disorders (e. g., schizophrenia); and (ii) the contribution of CNVs to disease etiology might be limited to specific bipolar disorder sub(pheno)types, particularly SAB and early age-at-onset cases.

In recent years, several whole-exome and whole-genome sequencing studies have been conducted in patients with bipolar disorder in order to identify rare, small-sized susceptibility variants (single-nucleotide variants, small insertions, and deletions). These studies investigated multiply affected families and unrelated case/control samples, and identified the first candidate genes for bipolar disorder [31]. At writing, no rare genome-wide significant sequence variants for bipolar disorder have yet been identified [20], possibly due to the still limited statistical power of these studies. However, the reported candidate genes showed an accumulation in specific pathways, including G-protein-coupled receptors [32]; postsynaptic density genes [33]; and neuronal ion channels, including GABA pathways [34]. An enrichment of rare variants was also found in genes in which *de novo* mutations have been detected in patients with schizophrenia and autism [35]. Furthermore, preliminary evidence suggests that *de novo* mutations might also contribute to the development of bipolar disorder, particularly in patients with an early age-at-onset [36, 37].

Molecular genetic findings in major depression

The largest GWAS of major depression to date have been conducted by large international consortia, using data generated from: (i) patients with a medically assigned diagnosis of major depressive disorder [12]; (ii) individuals with self-reported depression (e. g., [38]); or (iii) population-based samples (e. g., UK Biobank [39]). In total, these GWAS have analyzed data from hundreds of thousands of individuals. For major depression, larger sample sizes were required to identify genome-wide significant loci than was the case for bipolar disorder. A possible explanation for this is the lower heritability and greater etiological heterogeneity of major depression compared with bipolar disorder [20, 40].

A GWAS meta-analysis by the PGC investigated data from around 135,000 major depression patients and 345,000 controls, and identified a total of 44 independent, genome-wide significant loci [41]. More recently, Howard and colleagues [42] conducted a meta-analysis of the PGC GWAS data and additional GWAS data sets. This meta-analysis comprised data from 246,363 patients and 561,190 controls, and identified 102 independent genome-wide significant variants at 101 genomic loci [42]. The calculated SNP-based heritability for major depression was around 9 % [41]. In addition, major depression showed genetic correlations with a number of other diseases and phenotypes. Among others, these included other psychiatric disorders (e. g., bipolar disorder, schizophrenia, anorexia nervosa); the personality trait neuroticism; and metabolic and cardiovascular traits (e. g., coronary artery disease and waist-to-hip ratio) [41, 42].

Research has demonstrated that genomic loci and genes associated with major depression show an accumulation in specific pathways. These pathways include synaptic structure and activity [42], as well as neuron projection and genes encoding voltage-gated calcium channels [41].

Bioinformatic analyses of the GWAS data show that genetic correlations between clinically recruited major depression phenotypes, self-reported depression, and self-reported help-seeking behavior are high (≥85 %) [42]. However, other studies suggested that analyses based on "minimal phenotyping" definitions might lead to the identification of non-specific genetic factors that are common in major depression and other psychiatric diseases [43]. In addition, significantly higher major depression PRS were found in patients with an early disease onset, severe major depression, or recurrent episodes [41]. Altogether, these findings suggest that the results of large-scale GWAS with different phenotype definitions might not be generalizable for all patients [5] and that individual associated loci might only be relevant for a subset of cases.

In addition to large meta-analyses of broad depression phenotypes, GWAS have thus also been performed for specific disease sub(pheno)types, and have generated important insights into their respective biological basis (e. g., major depression with atypical features such as increased appetite and/or weight [44]). Power et al. performed a GWAS for major depression involving stratification for age-at-onset, and reported one replicated genome-wide significant locus for adult-onset major depressive disorder (>27 years [6]). Furthermore, the PRS analyses suggested differences in genetic susceptibility between adult- and earlier-onset major depressive disorder, with earlier-onset patients showing a stronger genetic overlap with bipolar disorder and schizophrenia cases [6].

In an investigation of the contribution of rare CNVs to the development of major depressive disorder, Zhang and colleagues reported an enrichment of short deletions

(<100 kilobases) in patients compared with controls [45]. The association was mainly driven by intergenic deletions, which suggests that disease risk might be mediated by the disruption of regulatory elements [45].

Using a sample of around 24,000 depression cases and 383,000 controls from the UK Biobank [46], Kendall and colleagues investigated associations between depression risk and 53 CNVs that had shown association with neurodevelopmental disorders in previous research. The authors demonstrated an association between the combined set of 53 neurodevelopmental CNVs and self-reported depression. Individual analysis of the 53 CNVs revealed that three CNVs were significantly associated with self-reported depression after Bonferroni correction for multiple testing. These comprised the 1q21.1 duplication; the duplication of the Prader–Willi syndrome region on chromosome 15; and the 16p11.2 duplication [46], which has previously been associated with bipolar disorder [28].

At writing, few next-generation sequencing studies have been conducted in patients with major depression. However, these studies identified the first candidate genes for major depression, and suggested a contribution of specific pathways to disease development, including sphingolipid metabolism [47]; cholesterol biosynthesis [48]; and transforming growth factor beta signaling [49].

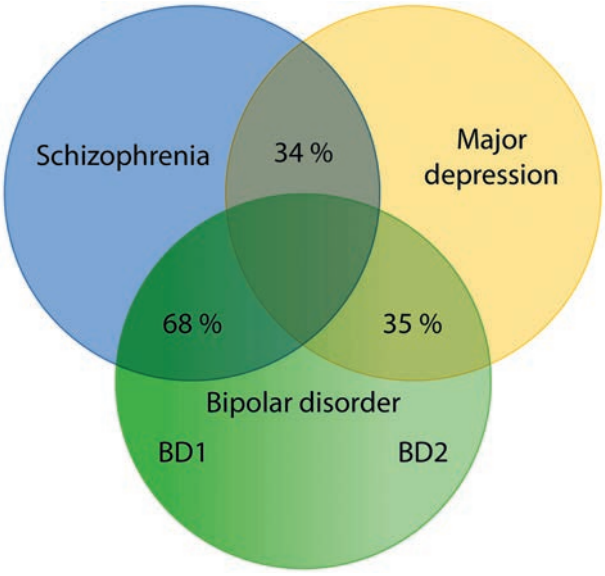

Figure 1: Genetic overlap between bipolar disorder, major depression, and schizophrenia.

Genetic correlation data were obtained from [53]. Abbreviations: BD1, bipolar disorder type I; BD2, bipolar disorder type II.

Genetic overlap

Bipolar disorder and major depression show a substantial overlap in terms of clinical symptoms [50]. In addition, both disorders co-occur in families, and full siblings of bipolar disorder patients show an increased relative risk of 2.1 for the development of major depression [14]. A plausible hypothesis therefore is that a proportion of the underlying genetic factors might overlap and contribute to the etiology of both diseases. From a methodological perspective, quantification of a genetic overlap between two disorders/phenotypes is a challenging undertaking. Nevertheless, this has been achieved using large GWAS data sets and innovative statistical methods (e. g., [51, 52]). Research has demonstrated a strong genetic overlap between bipolar disorder and major depression, as quantified at around 35 % [53]. As stated above, affective disorders show extensive genetic overlap with other psychiatric disorders, in particular schizophrenia (around 34–68 % [53], Figure 1). Recently, Coleman and colleagues performed a GWAS meta-analysis of data on around 185,000 affective disorder patients and 440,000 controls, and identified 73 genome-wide significant loci [50]. Interestingly, the results of the affective disorder meta-analysis showed a greater similarity to those of the major depression analyses than those obtained for bipolar disorder. A possible interpretation of this finding is that depressive symptoms are the unifying feature of the affective disorder spectrum [50].

Outlook

Key strategies for the generation of further insights into the genomic basis of the affective disorders will be the further enlargement of genomic data sets and data merging within large international consortia. In GWAS, this will lead to the identification of new, disease-associated loci and the most relevant biological pathways [54]. At the level of rare variants, larger data sets will be required to identify rare sequence variants at the level of genome-wide significance [55].

The face-to-face recruitment of patients and controls within the clinical setting is a time-consuming process. Thus, to achieve the large sample sizes required for the identification of further common and rare risk variants, alternative recruitment strategies are now being considered. These include the online recruitment of patients with affective disorders and the collection of questionnaire-based phenotype data (e. g., [56]). However, as mentioned above,

it should be considered that the inclusion of individuals based on "minimal phenotyping" definitions might lead to the identification of non-specific genetic risk factors [43]. To reduce heterogeneity, other research approaches focus on particularly severely affected cases, e. g., patients with severe depression who require electroconvulsive therapy [57]. The relevance of these two different strategies (i. e., maximizing sample size by combining data from different phenotype assessment modalities versus a focus on more clinically homogenous subtypes) has been discussed elsewhere [58]. Briefly, it can be concluded that both approaches will be important in terms of unraveling the genetic architecture of the affective disorder spectrum [58].

Previous genetic studies on affective disorders were predominantly based on European samples [5, 17]. For other ethnicities, an increasing number of analyses have already been published (e. g., [59, 60]), but large-scale studies are still largely lacking. It is therefore important to promote the recruitment of non-European samples and their inclusion in large international consortia, which will also facilitate the assessment of the generalizability of genetic findings obtained from samples of European origin [54]. Although most genetic associations are likely to be observed across different ethnicities, there might also be population differences, so that the global application of the PRS (see below) requires risk allele weights derived from different ancestral populations [54].

As a consequence of the clinical and genetic findings described above, psychiatric disorders are increasingly being conceptualized using dimensional approaches [61], rather than as categorical diagnoses. Recently proposed models view affective disorders as representing a combination of multidimensional and longitudinal symptom domains (e. g., activity, cognition, and emotion [62]). The definition of novel, biologically informed groups (so-called "biotypes") requires transdiagnostic research approaches that investigate different symptom dimensions in patients with affective disorders and controls in a longitudinal manner (e. g., [63, 64]).

Transdiagnostic analyses also facilitate understanding of the biological basis of cross-disorder subphenotypes. Recently, for example, Mullins and colleagues performed a GWAS of suicide attempt in patients with bipolar disorder, major depressive disorder, and schizophrenia [65]. In this study, the PRS for major depression were significantly associated with suicide attempt in all three diagnostic categories, suggesting that the PRS could be used to distinguish between patients with different symptom profiles [65].

In addition to the discovery of new genetic risk factors, functional analysis of the already identified genomic loci is required to elucidate the underlying pathomechanisms and unequivocally pinpoint the disease-associated genes or regulatory elements [54]. This will require an extensive use of diverse methods, e. g., analyses of animal models or induced pluripotent stem cells [66]. For the latter analyses, approaches that take into account the cumulative contribution of common variants using PRS have been proposed [67]. Another promising approach to the identification of disease-relevant genes at the associated loci is the combining of GWAS data with transcriptomic and expression quantitative trait loci data sets (e. g., the Genotype-Tissue Expression Project [68] and the CommonMind Consortium [69]). Here, innovative statistical analyses of the GWAS data can lead to the identification of disease-relevant tissues and cell types. In affective disorders, analyses performed to date have implicated diverse brain regions and specific cell types, such as dopaminergic neuroblasts and medium spiny neurons [50].

Another increasingly relevant field of molecular genetic research is pharmacogenetics. This field investigates the influence of genetic factors on the efficacy or side effects of drugs [70]. To date, pharmacogenetic studies have focused on individual drugs for specific diseases. In an investigation of bipolar disorder, a locus on chromosome 21 showed a genome-wide significant association with the lithium response [71]. In major depression, numerous candidate genes have already been implicated in the response to selective serotonin reuptake inhibitors (e. g., [72, 73]). Further studies are warranted to investigate the molecular mechanisms that underlie these findings and to evaluate their potential clinical utility [71].

The development of an affective disorder is based on complex interactions between genetic and environmental factors. Continuous elucidation of the contributing genetic factors enables the investigation of specific gene–environment interactions [20, 74]. In recent years, research has identified molecular signatures of environmental factors in disease-relevant cells and tissues, e. g., via the analysis of DNA methylation (e. g., [20, 75, 76]). As a result of technological advances, such as methylation arrays, systematic genome-wide analyses of several hundred thousand CpG sites are now feasible. In a recent study, the use of methylation arrays in epigenome-wide association analyses of depressive symptoms led to the identification of three significantly associated methylation sites [77], which implicate axon guidance in disease development. These findings demonstrate that epigenetic analyses can generate additional key insights into the underlying molecular mechanisms of affective disorders.

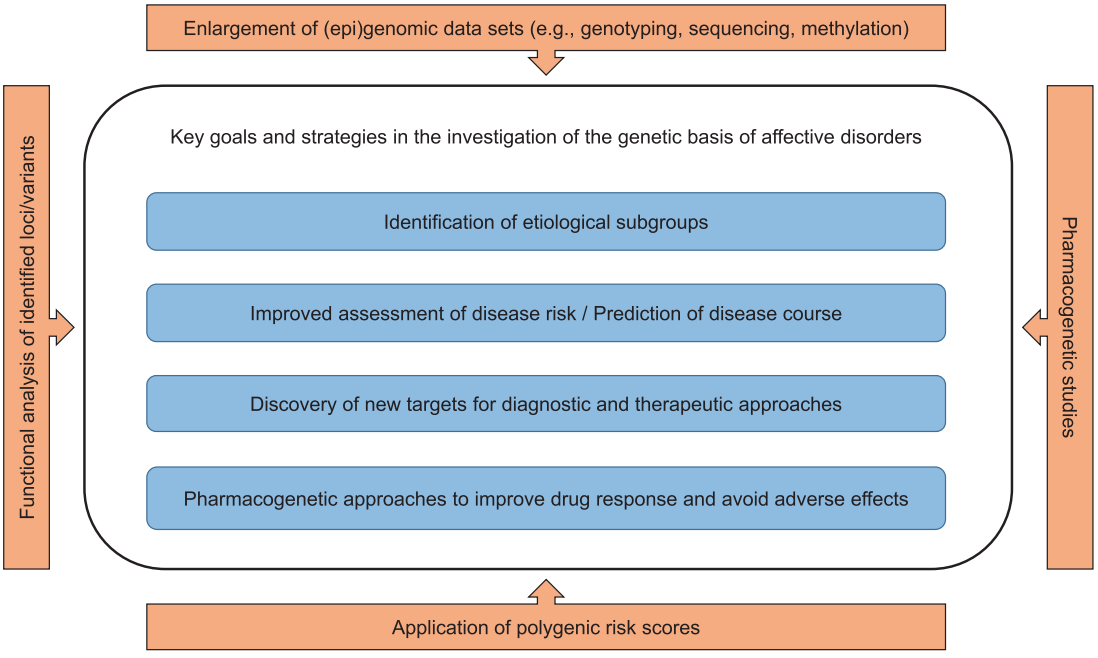

Figure 2: Key goals and research strategies in the investigation of the genetic basis of affective disorders.

Application of genetic findings in clinical practice

The findings of molecular genetic studies offer great potential in terms of improving the future clinical management of affective disorder patients. Over the next decade, diverse research approaches are expected to generate further insights into the etiology of the affective disorders. Key goals and strategies in the investigation of the genetic basis of affective disorders are summarized in Figure 2.

The application of the PRS promises opportunities for the identification of etiological subgroups and the prediction of disease risk/course. For example, in the major depression GWAS of the PGC [41], individuals were grouped into PRS deciles, and odds ratios for disease status were calculated for each decile relative to the lowest-risk decile. The odds ratios increased with a greater number of major depression risk alleles, and an odds ratio of 2.4 was observed in the tenth versus the first PRS decile [41], which suggests that the use of PRS allows the stratification of individuals according to their disease risk. In the long term, one conceivable application of PRS in affective disorders would be an improved differentiation between a unipolar and a bipolar disease course, since around 40 % of bipolar disorder patients are initially diagnosed with major depression [78, 79]. The early prediction of disease course might also be clinically relevant, since research has shown that patients who are ultimately diagnosed with bipolar disorder are less likely to respond to antidepressant treatment for an acute depressive phase than patients with purely major depression [80]. The results of future studies into genetic differences between bipolar disorder and major depression could be used in conjunction with other parameters (e. g., questionnaires, imaging data) to generate more accurate estimates. At present, PRS are not suitable for use as diagnostic or predictive tests for affective disorders, as they still explain too little of the observed phenotypic variance [70]. However, the predictive value of the PRS is likely to be increased in the future by the inclusion of additional common (and rare) variants. The general conditions for the application of genetic testing in psychiatric disease, including the affective disorders, are the subject of intensive ongoing discussion. An overview of these discussions is provided in the Genetic Testing Statement of the International Society of Psychiatric Genetics (https://ispg.net/genetic-testing-statement/).

Data from molecular genetic studies may facilitate the identification of targets for the development of new therapeutic approaches [81]. Analysis of GWAS data for major depression [41] using innovative bioinformatic methods has shown that more than 20 significantly associated genes outside the major histocompatibility complex are “druggable” [82]. Furthermore, the authors found that several drug classes showed a significant enrichment of associations, including calcium channel blockers, antipsychotics, and antihistamines [82]. Although these results re-

quire both validation in model systems and clinical evaluation, they illustrate the major potential of GWAS as a source of new therapeutic approaches for bipolar disorder, major depression, and other forms of psychiatric disease [82].

Conclusions for research and clinical practice

- Bipolar disorder and major depression are multifactorial diseases, which are caused by a complex interplay of multiple genetic and environmental factors.
- Large GWAS of affective disorders have shown that common genetic variation explains a substantial fraction of the phenotypic variance. The precise pathophysiological mechanisms of the associated genetic factors remain largely unknown. The functional analysis of these mechanisms is an important task for future research.
- The identification of rare variants with large effects remains in its infancy. However, researchers anticipate that in the near future, next-generation sequencing studies in large patient and control samples will generate statistically significant and replicable results.
- The results of genomic and subsequent functional investigations will improve our understanding of the biological basis of the affective disorders. This in turn will facilitate the development of new preventative, diagnostic, and therapeutic approaches.

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Patients' rights and animal protection statements: For the present article, the authors have not conducted any studies with human or animal subjects. For the presented studies, the ethical guidelines given there apply.

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