

Decoding the Genetics and Underlying Mechanisms of Mood Disorders

Sevilla D. Detera-Wadleigh and Takeo Yoshikawa

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Bipolar disorder and major depression are common debilitating mood disorders. The latest World Health Organization’s World Mental Health Survey Initiative estimated the median and inter-quartile lifetime prevalence for mood disorders to be 3.3–21.4% (Kessler et al. 2007). In Global Burden of Disease surveys, depression has been estimated to be a leading cause of disability worldwide and is projected to be a major cause of morbidity in 2030 (first in high income countries, second in medium income countries and third in low income countries) (Mathers and Loncar 2006). A recent study has reported that the rise of high levels of psychological stress in the workplace seems to precipitate depression and generalized anxiety disorders (Melchior et al. 2007). Taken together, these suggest that mood disorders impose an enormous burden on families, society and the health care system. Reducing

S.D. Detera-Wadleigh (✉)
Genetic Basis of Mood and Anxiety Disorders, Mood and Anxiety Disorders Program,
National Institute of Mental Health Intramural Research Program, National Institutes of Health,
Bethesda, MD 20892, USA
deteras@mail.nih.gov

this burden may require improved diagnostic precision and treatment modalities, preventive measures and greater public awareness. A key element in achieving this goal involves the discovery of genetic and environmental factors that contribute to disease risk. So far, from a combination of approaches evidence for risk-conferring variation in various genes has emerged although further confirmation is needed and functional relevance has to be established. This chapter will focus on strategies designed to clarify the genetics and underlying mechanisms of mood disorders, and discuss progress in this endeavor and the challenge that remains.

1 Introduction

The diagnosis for mood disorders is based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association 1994). The DSM-IV categories of mood (affective) disorders are shown in Table 1. The third and fourth editions, DSM-III and DSM-IV, have been used in many published genetic studies in mood disorders for the past decade.

Table 1 Mood disorders (DSM-IV)

1. Depressive disorders
• Major depressive disorder
◦ Single episode
◦ Recurrent
• Dysthymic disorder
• Depressive disorder not otherwise specified (NOS)
Examples
• Minor depressive disorder
• Recurrent brief depressive disorder
• Postpsychotic depression of schizophrenia
2. Bipolar disorders
• Bipolar I disorder
◦ Single manic episode
◦ Most recent episode hypomanic
◦ Most recent episode manic
◦ Most recent episode mixed
◦ Most recent episode depressed
◦ Most recent episode unspecified
• Bipolar II disorder (recurrent major depressive episodes with hypomania)
3. Cyclothymic disorder
4. Bipolar disorder not otherwise specified (NOS)
Examples
• Recurrent hypomania without depression
• Manic episode superimposed on delusional disorder
5. Mood disorder due to a general medical condition
6. Substance-induced mood disorder
7. Mood disorder not otherwise specified (NOS)

Recently, in reviewing the evolution of the DSMs, Hyman (2007) discussed the need to enhance diagnostic precision and the value of incorporating relevant knowledge in neurobiology as they relate to psychiatric disorders. The DSMs define psychiatric diseases as categorical entities but “many mental disorders may be better conceptualized as dimensional traits” (Hyman 2007). The standardized guidelines in the DSMs are based mainly on clinical observation and they lack biological or quantitative measures for specific clinical phenotypes. It follows that there is a need to refine phenotype classification. Furthermore, the DSMs do not address the possibility that either bipolar disorder or major depression is a clinical consequence of various diseases defined by varied or independent sets of etiologic determinants.

Mood disorders display a complex pattern of inheritance and their genetic architecture remains elusive. These diseases are thought to be genetically heterogeneous both at the locus and allelic levels. One well-accepted proposal that attempts to explain etiology is the common disease–common variant (CDCV) hypothesis that predicts the central role of multiple modest-effect variation (Reich and Lander 2001) (Fig. 1). Statistically significant signals from minor-effect loci are inherently more difficult to detect and/or replicate, requiring thousands of samples of identical or similar ethnic background. Furthermore, it is unclear how many modest-effect variants are necessary and sufficient to account for the high heritability of, and impairment of function in individuals with, mood disorders.

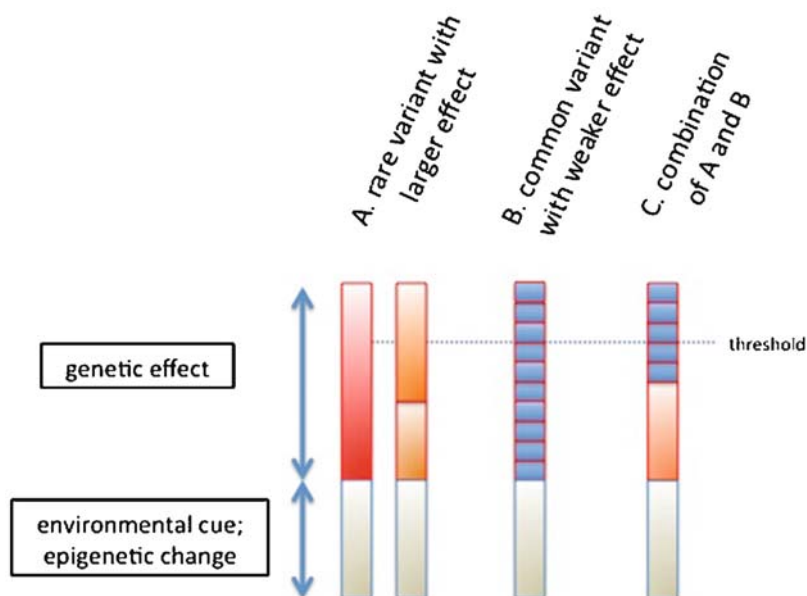


Fig. 1 Proposed genetic architecture for complex diseases, e.g., Mood disorders. Shown are the potential role of common variants, rare variants, a combination of common and rare variants, and the impact of epigenetic factors and environmental cues on these alleles. Boxes and squares are not drawn to scale

Potentially, subtle structural changes in the genome may confer greater sensitivity to environmental cues and thus act as “first responders”. Conceivably, what is statistically measured as “small effect” may not be reflected as “minor” inside the cell, as perturbed cascades of reactions and interacting networks magnify the subtle effect and confer a pronounced biological defect.

An alternative hypothesis for the allelic blueprint of complex disease invokes the fundamental role of rare variants (Pritchard 2001). Potentially, infrequently occurring high penetrance alleles may be detectable in large, extended families and/or in population isolates. In these families, one or a few high penetrance variants could account for a large proportion of risk and heritability (Fig. 1). A recent study that evaluated rare single nucleotide polymorphisms (SNPs) in HapMap, ENCODE and SeattleSNPs with minor allele frequency (MAF) of 0.5%, showed that low MAF was predictive of functional alteration and that lower MAF of nonsynonymous SNPs correlated inversely with increased likelihood of disruption of protein function (Gorlov et al. 2008). This led the authors to propose a vital role for “slightly deleterious” rare SNPs, many of which remain to be identified. Simulations showed that thousands of samples are required to achieve reasonable power to detect these SNPs, with MAF ranging from 1 to 5% (Gorlov et al. 2008).

A similar model dubbed “common disease–rare alleles” has been proposed as a possible etiologic scenario for schizophrenia (McClellan et al. 2007). This paradigm draws upon the potential role of multiple rare, new, mutations in individual or few families, variation that might have occurred in the germ line as a consequence of population expansion. As shown in Alzheimer’s disease, risk is due to rare major-effect high-penetrance in some families and common alleles in most families (Fig. 1). Also, the collective effect of multiple rare alleles in several candidate genes contribute to low levels of plasma HDL cholesterol, a quantitative trait which is heritable and displays a complex mode of transmission (Cohen et al. 2004). It is further speculated that infrequent, highly penetrant, alleles could be found in genes that have common associated variants or they could be embedded within associated common haplotypes. In this instance, deep resequencing in cases needs to be done to detect the rare-risk-conferring variants.

Several strategies are being employed to begin to untangle the genetic etiology of mood disorders (Fig. 2). In the past decade, the most popular approach has been genetic linkage mapping or positional cloning which has been exceedingly successful in localizing causative genes for monogenic disorders. In mood disorders, linkage analysis has been employed as an initial approach toward vulnerability locus identification but, as will be discussed in later sections, linkage for mood disorders has been only modestly compelling.

Very recently, genome-wide association studies (GWAS) have become feasible and thus the favored approach for genetic analysis of complex disease. The rapid explosion of published articles on GWAS in complex diseases is underpinned by recent technological progress. Advances in high throughput genotyping technology facilitate rapid comprehensive surveys of the entire genome with up to a million SNPs on thousands of samples. Although the cost of high throughput genotyping via chip arrays (e.g., Affymetrix: www.affymetrix.com; Illumina, Inc: www.illumina.com)

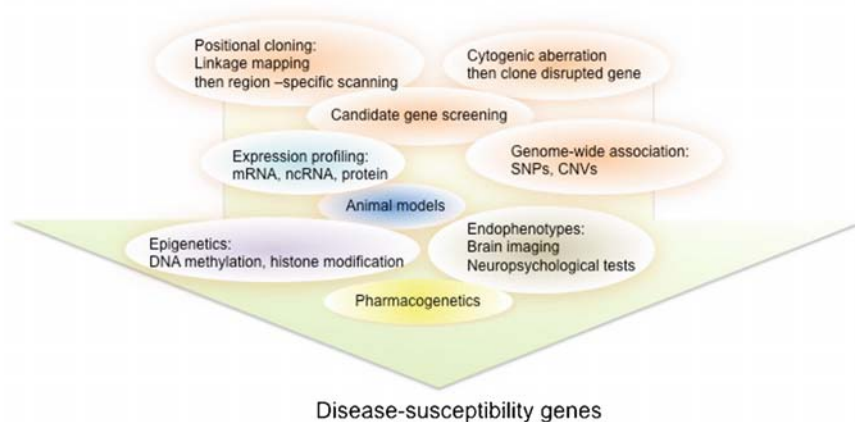


Fig. 2 Strategies to dissect the underlying genetic basis for mood disorders. Genome-wide association studies have grown exponentially very recently. All strategies are discussed in the text

has been declining, it is still beyond the reach of most laboratories. To address this problem, a public–private effort was launched in the United States. The Genetic Association Information Network (GAIN; http://www.fnih.org/GAIN2/home_new.shtml) (2007), a partnership composed of the National Institutes of Health (NIH) Foundation, NIH and Pfizer Global Research and Development was formed to help unravel “the genetics of common disease through whole genome association studies”. GAIN is supporting GWAS of several complex diseases, including bipolar disorder and major depression. Independently, in the U.K., the Wellcome Trust Foundation has funded GWAS screens of bipolar disorder and six other common diseases (The Wellcome Trust Case-Control Consortium 2007). Genotyping of bipolar disorder and major depression samples by GAIN has been completed. Both initiatives are making data available to the research community. Easy access by more researchers should hasten the discovery of disease-predisposing genetic factors and stimulate investigations into pathways involved in pathogenesis.

2 Bipolar Disorder

2.1 *Clinical Presentation and Epidemiology*

Bipolar disorder, also known as manic-depressive illness, is characterized by disabling episodic and recurrent swings of severe elation and depression (Table 1). In rare cases, patients show only recurrent manic episodes with no history of depression (“unipolar mania”). Patients with severe mania referred to as bipolar I (BPI) have markedly impaired social and occupational functioning and often need hospitalization. A milder form of mania, hypomania, is categorized as bipolar II (BPII).

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