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REVIEW

Genetics of affective (mood) disorders

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The enormous public health importance of mood disorders, when considered alongside their substantial heritabilities, has stimulated much work, predominantly in bipolar disorder but increasingly in unipolar depression, aimed at identifying susceptibility genes using both positional and functional molecular genetic approaches. Several regions of interest have emerged in linkage studies and, recently, evidence implicating specific genes has been reported; the best supported include BDNF and DAOA but further replications are required and phenotypic relationships and biological mechanisms need investigation. The complexity of psychiatric phenotypes is demonstrated by (a) the evidence accumulating for an overlap in genetic susceptibility *across* the traditional classification systems that divide disorders into schizophrenia and mood disorders, and (b) evidence suggestive of gene-environment interactions.
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Mental disorders in general, and mood disorders in particular, are leading causes of morbidity which affect human populations around the world.[1] Mood (affective) disorders are the most common severe psychiatric disorders of adult onset. The term 'affective disorder' includes a wide variety of conditions, from mild and common mood variations to some of the most severe episodes of psychotic illness seen in clinical practice. Cooccurrence of other clinical syndromes (such as anxiety or substance abuse) is common. Genetic factors are known to play an important role in influencing susceptibility to all these illnesses.[2] Here, discussion will be restricted to the more severe end of the diagnostic spectrum; the diagnostic categories of bipolar disorder (in which most work has been done to date) and unipolar major depressive illness.

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Diagnostic issues

Affective disorders are complex genetic disorders in which the core feature is a pathological disturbance of mood ranging from extreme elation or mania to severe depression. Other symptoms also found in these disorders include disturbances in thinking and behaviour, which may include psychotic symptoms, such as delusions and hallucinations. Historically, affective disorders have been classified in a number of ways, with distinctions between endogenous and reactive episodes, psychotic and neurotic symptomatology and affective disorders arising *de novo* (primary) and those episodes arising in the context of another disorder (secondary).[3,4] The main nosological division in modern classification systems such as ICD10[5] or DSMIV[6] is between the unipolar and bipolar forms of the condition. The diagnosis of bipolar disorder (also known as manic depressive illness) requires that an individual has suffered one or more episodes of mania with or without episodes of depression at other times during the life history. This requirement for the occurrence of an episode of mania at some time during the course of illness distinguishes bipolar disorder from unipolar disorder (also commonly known as unipolar major depression, or simply unipolar depression) in which individuals suffer one or

more episodes of depression without ever experiencing episodes of pathologically elevated mood. Although bipolar and unipolar disorders are not completely distinct nosological entities their separation for the purposes of diagnosis and research is supported by evidence from outcome, treatment and genetic studies.[4,7] In DSMIV, bipolar disorder is subclassified into Bipolar I Disorder, in which episodes of clear-cut mania occur, and Bipolar II Disorder, in which only milder forms of mania (so-called 'hypomania') occur. Although there is evidence to support this distinction (eg, Simpson *et al*[8]), the validity of this subclassification awaits robust validation. The lifetime prevalence of narrowly defined bipolar disorder is in the region of 0.5–1.5% with similar rates in males and females and a mean age of onset around the age of 21 years.[9]

Unipolar disorder is substantially more common than bipolar illness but measured prevalence rates differ markedly according to the diagnostic criteria, methodology and sample employed. For example, the large US multisite Epidemiological Catchment Area (ECA) study reported a lifetime population prevalence for DSMIII major depression of approximately 4.4%,[10] whereas the US National Comorbidity Survey estimated the lifetime prevalence of DSM IIIR major depression to be 17.1% with 10.3% of the population experiencing a major depressive episode in the preceding 12 months.[11] In contrast to bipolar illness, the rate of unipolar disorder for women is about twice that for men – 21.3 and 12.7%, respectively, in the US National Comorbidity Survey,[11] and this gender difference is a consistent finding, at least in studies in the developed world. Affective disorders are associated with high levels of service utilisation and morbidity and often prove fatal, with up to 15% of patients eventually committing suicide.[12] Reasonably effective treatments are available for both manic and depressive episodes,[13] but current treatments have undesirable side-effects, are not effective in all patients and the pathogenesis of affective disorders remain poorly understood. These facts act as a major motivation for genetic investigation of affective illness with its promise of improved understanding of aetiology and more effective treatments.

Classical genetic epidemiology of mood disorders

Many classical genetic studies of mood disorders have been undertaken. Prior to the mid-1960s family studies of mood disorder did not make the bipolar/unipolar distinction. However, these studies provided evidence for familial aggregation of the broad mood disorder phenotype (reviewed by Tsuang and Faraone[14]). Subsequent family studies have provided persuasive evidence of familial aggregation of both bipolar and unipolar disorder; twin and adoption studies point to genes as an important cause of this familial resemblance.[15–17] In all, there is a consistent and impressive body of evidence that supports the existence of mood disorder susceptibility genes. These studies also demonstrate a graduation in risk of mood disorder between various classes of relatives with monozygotic co-twin showing highest risk, through first degree relative to unrelated member of the general population showing the lowest risk. As result of differences in methodologies and diagnostic classifications, the absolute measures of estimated lifetime risk vary between studies. Table 1 shows a representative range of estimates for relative risks and heritabilities. These data are consistent with models of inheritance that include multiple genes that interact with each other and environmental factors to confer susceptibility to illness (for example, Craddock *et al*[18]).

Table 1 Genetic epidemiology of mood disorders

	Bipolar disorder	*Unipolar depression*
Recurrence risk in sibling of a proband (λ_S)	5–10	2.5–3.5
Proband-wise MZ twin concordance (%)	45–70	40–50
Heritability estimate (%)	80–90	33–42

Linkage studies in bipolar disorder

Systematic genome screens have been reported on a variety of sample sets, ranging from large densely affected pedigrees in genetic isolates to large numbers of affected sibling pairs. The pattern of findings emerging is consistent with there being no gene of major effect to explain the majority of cases of bipolar disorder, but several regions have been implicated repeatedly by individual studies (but usually not sufficiently consistently to be highlighted by meta-analyses).

Two meta-analyses of bipolar disorder genome scans have been conducted. Badner and Gershon,[19] found the strongest evidence for susceptibility loci on 13q and 22q when examining seven published genome scans for bipolar disorder. However, the more recent and detailed meta-analysis of Segurado *et al*,[20] conducted using the bin-ranking methodology did not find genome-wide significant evidence for linkage but provided a more modest level of support for regions on chromosomes 9p22.3–21.1, 10q11.21–22.1, 14q24.1–32.12 and regions of chromosome 18. This meta-analysis demonstrated lesser consistency in the findings from bipolar scans than from schizophrenia scans.[21] Possible causes for these differences are discussed elsewhere.[22]

Since publication of the meta-analyses several further genome-wide scans in independent samples have been published, with several regions identified that meet

genome-wide significant or suggestive evidence for linkage. Of particular note is the 6q21–q25 region which was not implicated in either meta-analysis, but which is supported by one genome-wide significant[23] and three genome-wide suggestive signals,[24–26] making it one of the best-supported regions for bipolar disorder. Indeed, in the recent combined collaborative analysis of 11 bipolar linkage scans, this region achieved genome wide significance.[27]

Figure 1 shows chromosomal regions that have received genome-wide significant support in at least one scan. Of particular note are the 6q21–q25 region mentioned above and the 12q23–q24 region, which has two genome scans reporting genome-wide significance[25,28] and is also supported by linkage analysis in unipolar disorder (see below).

Gene studies of bipolar disorder

To date there has not been unambiguous demonstration of a susceptibility gene identified for bipolar disorder by positional cloning. Potentially interesting findings have come from the study of functional candidates and, most recently, investigation of genes first implicated in schizophrenia (some of which map in linkage regions of interest in bipolar disorder). However, none of the findings yet achieve the level of support that *dysbindin* and *NRG1* have received in schizophrenia.[22]

Functional candidates

Most studies in the literature have focussed on neurotransmitter systems influenced by medications employed in the management of the disorder, particularly the dopamine, serotonin and noradrenaline systems (reviewed by Craddock *et al*[29]). These are not predicated on a sophisticated level of hypothesis or understanding of pathogenesis. For most genes studied, the usual pattern has been for one or a few positive studies along with an even greater number of negative replications. However, at least some meta-analyses of polymorphisms of known functional relevance in three of the genes are significant at the $P<0.05$ level – *MAOA*,[30] *COMT*[31] and *5HTT*,[32,33] all with modest effect sizes (odds ratios, OR$\ll$2). It is of interest that *COMT* has also been implicated in schizophrenia[34] and has received support from the same group in a modestly sized study of bipolar disorder.[35] These findings remain to be tested in the independent, large samples that

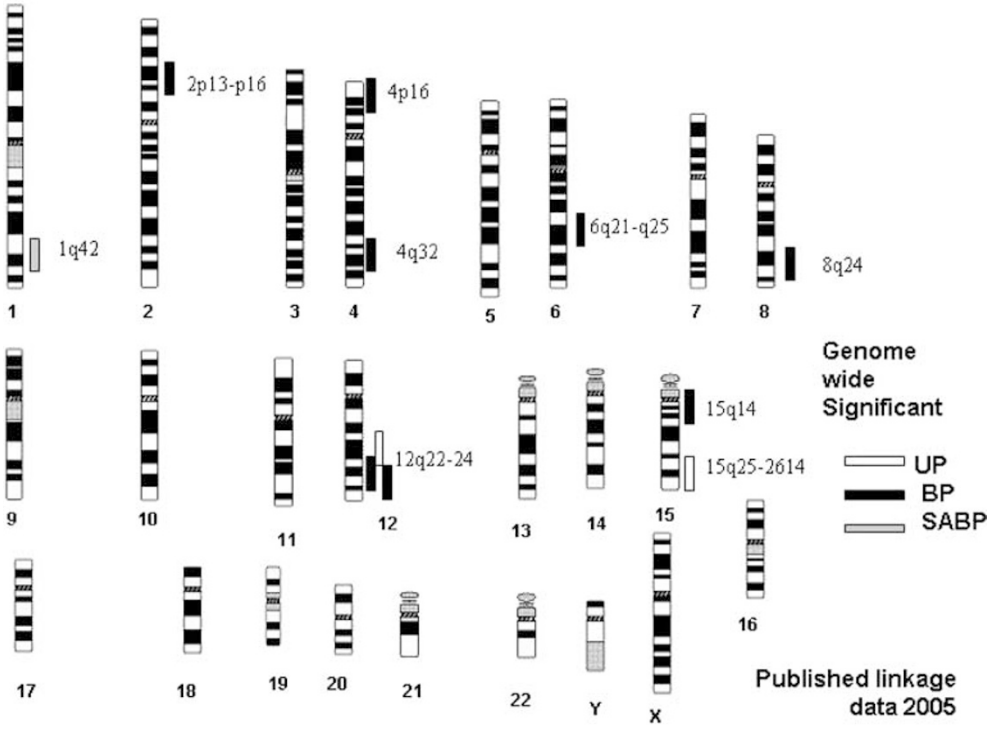

Figure 1 Chromosome ideograms showing locations of genome-wide significant linkages for mood disorder spectrum phenotypes. The *predominant* phenotype used in the analysis is shown as: UP: unipolar disorder; BP: bipolar disorder; SABP: schizoaffective disorder, bipolar type. Note that most genome scans of bipolar disorder have used a range of definitions of the bipolar phenotype from narrow (only Bipolar I disorder) to broad (including also bipolar II disorder, schizoaffective disorder and unipolar disorder).

will be required to determine unambiguously whether and to what extent variation within these genes contributes to susceptibility to bipolar disorder, or to some intermediate clinical phenotype.

Most of the candidate gene reports in the literature describe studies in modestly sized samples (a few hundred individuals), which are likely to be underpowered for plausible effects sizes. As for all complex disorders, the trend in candidate gene studies of bipolar disorder is for the use of larger samples, with increased power to detect modest or small effect sizes, and examination of candidate genes predicated on more sophisticated models of pathogenesis or directed by positional information from linkage studies. Recently, replicable positive findings have started to emerge from these approaches.

D-amino acid oxidase activator DAOA(G72)/G30 locus

At least five independent datasets contribute evidence that variation at the *DAOA/G30* locus on chromosome 13q influences susceptibility to bipolar disorder. This locus was implicated originally as being involved in susceptibility to schizophrenia.[36] It was a novel locus with a designation of G72. The locus was renamed as D-amino acid oxidase activator, DAOA, because biological studies suggested that the gene product activated the enzyme, D-amino acid oxidase (DAO); genetic evidence was also found in this original study for association of alleles at DAO with susceptibility to schizophrenia. Subsequently linkage disequilibrium (LD) at the DAOA locus was also reported with bipolar disorder in two US family samples[37] and this was replicated in a further US family sample,[38] German case–control sample,[39] and our own large UK case-control sample.[40] In all studies, evidence for LD came from individual single nucleotide polymorphisms (SNPs) as well as multilocus haplotypes, although there is variation between studies in the SNPs and haplotypes showing LD. No pathologically relevant variant has yet been identified and the biological mechanism remains to be elucidated. (It is of interest that *DAO* lies in the 12q23 region implicated in linkage studies of both bipolar and unipolar disorder (see Figure 1). *DAO* has been examined in only one study of bipolar disorder,[39] which found no evidence of LD. However, in view of the findings with DAOA, DAO warrants more thorough study in bipolar disorder).

Brain derived neurotrophic factor

A functional candidate gene that has attracted a great deal of recent interest is *brain derived neurotrophic factor* (*BDNF*).[41] BDNF is a member of the neurotrophin superfamily. Neurotrophins are synthesised in neurons as proforms that can be cleaved intra- or extracellularly and both their synthesis and secretion depends upon neuronal activity. BDNF plays an important role in promoting and modifying growth, development and survival of neuronal populations and, in the mature nervous system, is involved in activity-dependent neuronal plasticity.[42] These processes are prominent in the synaptic plasticity hypothesis of mood disorder, which focuses on the functional and structural changes induced by stress and antidepressants at the synaptic level. The *BDNF* gene lies on the reverse strand of chromosome 11p13 and encodes a precursor peptide (proBDNF), which is cleaved proteolytically to form the mature protein.[43] The 11p13 chromosomal location of *BDNF* has been implicated in some linkage studies of bipolar disorder, but not in meta-analyses of linkage studies.

Consistent with the strong evolutionary conservation of the *BDNF* coding sequence across species, only one frequent, nonconservative polymorphism in the human *BDNF* gene has been identified, a SNP at nucleotide 196 within the 5′pro-BDNF sequence that causes an amino acid substitution of valine to methionine at codon 66 (Val66-Met). There is cross-species conservation of the precursor portion of proBDNF, which is consistent with potential functional importance and, it is possible that, the common Val66Met polymorphism could itself have a functionally relevant effect by modifying the processing and trafficking of BDNF.[44]

There have been three positive reports using family-based association studies of Caucasian bipolar disorder samples of European-American origin and the Val66Met SNP: two were based on adult bipolar samples[45,46] and one was based on a small childhood onset sample.[47] All have shown overtransmission of the common Val allele. Evidence with multilocus haplotypes was stronger in one study.[46] There have been four case–control association studies (of European,[48,49] Chinese[50] and Japanese origin[51]) to date, in which there is no evidence for an allelic or genotypic association. In our own Caucasian bipolar case–control sample ($N = 3062$) we found no overall evidence of allele or genotype association. However, we found significant association with disease status in the subset of cases that had experienced rapid cycling, (four or more episodes per year) at some time, and a similar association on reanalysis of our previously reported family-based association sample.[52] This suggests that variation at the Val66Met polymorphism of *BDNF* may not play a major role in influencing susceptibility to bipolar disorder as a whole but, rather, may be associated with susceptibility to a specific aspect of the clinical bipolar phenotype. It should, however, be noted that the Val66Met polymorphism lies within a large haplotype block so it is difficult to determine which variant(s) within the block is (are) pathogenically relevant.

Substantial additional genetic and biological work will be required to confirm (or refute) the role of *BDNF* in influencing susceptibility to bipolar disorder. Systematic study of variation across the whole gene is required with study in further independent samples.

Other genes

From time to time, scientific journals and lay press have carried reports announcing discovery of 'bipolar genes'. (This terminology is, of course, a gross oversimplification and, based upon genetic epidemiology,[18] there are likely to be many susceptibility alleles). We will briefly mention three of these genes. Two of these are in the 22q chromosome linkage region of interest. *G-protein receptor kinase 3* (*GRK3)* was implicated through positional follow up of a linkage signal in a set of US pedigrees and was supported also by expression data in a rodent model of mania.[53] However, this has not yet received independent support. *XBP1*, a pivotal gene in the endoplasmic reticulum (ER) stress response, was reported to show association at a promoter polymorphism with bipolar disorder susceptibility in two small association samples.[54] Some degree of circumstantial biological support for a functional role for this polymorphism came from a cellular model of the action of mood stabiliser medications. However, this report is highly likely to be a type I error because the putative functionally relevant variant was found to have no influence on susceptibility in independent family-based and case–control association samples six times larger than those in the initial report.[55] More promisingly, but as yet not widely tested, is the report that *P2X7*, in the 12q24 region of linkage interest, influences susceptibility to both bipolar disorder and unipolar depression.[56]

Linkage studies in unipolar disorder

Family members of bipolar probands who themselves suffer with unipolar depression have been included in the broad phenotype in most studies of bipolar disorder. However, compared with bipolar disorder and schizophrenia, relatively few genome scans of unipolar disorder *as the main phenotype* have been conducted to date and there have been no meta-analyses undertaken. However, genome-wide signals have been reported (see Figure 1). One of the regions of interest, 12q22–23 overlaps with a region of interest in bipolar disorder (two genome-wide significant signals) and finds modest support in a large sibling pair genome scan of unipolar depression.[57] Further, this region is also implicated by two pedigrees that segregate both bipolar spectrum mood disorder and Darier's disease (an autosomal dominant skin disease caused by mutations at ATP2A2 which maps at 12q23–q24.1) showing maximum LOD >4 at markers in this region.[58–60] It is also of interest that a large genome scan of anxiety traits produced its strongest (and genome-wide significant) linkage signal in this same region of 12q.[61]

A study by Zubenko *et al*[62] of recurrent early onset depression identified a surprisingly large number of linkage signals but it is difficult to interpret the statistical significance; the strongest signal was at 2q close to the gene encoding CREB1. A theme that seems to be emerging from this and other linkage studies of unipolar disorder is a gender-specificity in linkage signals. For example, the 12q signal in the study of Abkevich *et al*[63] was present only in males; the 2q signal of Zubenko *et al*[62] was present only in females. These findings await replication.

Linkage studies have also been undertaken in which the clinical phenotype has included unipolar depression as a major component, together with other comorbid (and putatively pathogenetically related) psychiatric phenotypes such as alcohol abuse[64] and anxiety.[65]

Gene studies in unipolar disorder

As with linkage studies, to date, less attention has been given to genetic association studies of unipolar disorder than has been the case for bipolar disorder or schizophrenia. There are no unambiguous positive findings but the literature is developing rapidly. Given the expected smaller effect sizes and the possibility of greater clinical heterogeneity in unipolar disorder compared with bipolar disorder and schizophrenia, it can be expected that larger samples are likely to be required both for detection and replication of susceptibility loci. Perhaps the most interesting finding to emerge to date is the report of interaction between a functional variant at the serotonin transporter gene and the occurrence of life events in early adulthood.[66] There have been both positive[67] and negative[68] attempts at replication. It is widely assumed that gene-environment interactions and coaction will occur in mood disorder and this finding may prove to be the first such example, although robust replication is required.

Closer attention to the phenotype: clinical covariates and subtypes

As discussed elsewhere,[15] mood disorder researchers have been taking an interest in a variety of clinical sub-types and covariates over recent years, as a way of testing subsets of cases with increased clinical (and hopefully genetic) homogeneity. Examples include rapid cycling,[69] lithium responsiveness,[70] bipolar affective puerperal psychosis (triggering of bipolar episodes in females by parturition),[71,72] early age at onset[73] and occurrence of psychotic features during illness.[74–76]

Consideration of the occurrence of psychotic features in bipolar disorder brings us to consider the interesting and biologically important issue of the overlap in genetic findings in bipolar disorder and schizophrenia.

The overlap in findings between bipolar disorder and schizophrenia

Traditionally psychiatric research in general, and the search for predisposing genes in particular, has proceeded

under the assumption that schizophrenia and mood disorder are separate disease entities with separate underlying aetiologies (and treatments) – the so-called 'Kraepelinian dichotomy'. This distinction has pervaded Western psychiatry since Emil Kraepelin's influential nosological writings[77] and survives in current operational classification systems such as ICD10[5] and DMSIV,[6] although some workers, such as Crow, have argued for a continuum approach to psychosis.[78] The clinical reality is that many individuals with severe psychiatric illness have features that fall between these two 'extremes' and have *both* prominent mood and psychotic features (often classified as 'schizoaffective disorder' or some similar atypical diagnosis). This suggests that there may not be a neat biological distinction between schizophrenia and bipolar disorder. This possibility finds support in several observations from genetic research, including the following:

Family studies

Although schizophrenia and bipolar disorder may 'breed true',[79–81] families are known within which there are multiple cases of schizophrenia, bipolar disorder, and cases with both psychosis and mood disorder.[82] Further, some studies have shown statistically significant evidence that bipolar disorder occurs at an increased rate in the relatives of probands with schizophrenia[83] and that bipolar disorder occurs at an increased frequency in the relatives of bipolar probands.[84] Schizoaffective disorder has been shown to occur at an increased rate in the families of probands with schizophrenia,[85] and in the families of probands with bipolar disorder.[86] Both schizophrenia and bipolar disorder have been shown to occur at increased rates in the families of probands with schizoaffective disorder.[86] Together, these data suggest a more complex relationship between the psychoses than is reflected in the conventional dichotomous view.

Twin studies

Only one twin study has used an analysis that was unconstrained by the diagnostic hierarchy inherent in current classification systems (ie the principle that schizophrenia 'trumps' mood disorder in diagnosis). This study demonstrated a clear overlap in the genetic susceptibility to syndromally-defined mania and schizophrenia.[87] The findings suggested the existence of some susceptibility genes that are specific to schizophrenia, others that are specific to bipolar disorder and yet others that influence susceptibility to schizoaffective disorder, schizophrenia and bipolar disorder.

Linkage studies

Genetic linkage studies have identified some chromosome regions that show convergent or overlapping regions of interest in bipolar disorder and schizophrenia, including regions of 13q, 22q, 18[19,88] and 6q. The hypothesis that loci exist that influence susceptibility across the schizophrenia-bipolar divide, receives further support from the observation that a genome scan, using families ascertained on the basis of a proband with schizoaffective disorder (a form of illness with prominent features of both schizophrenia and bipolar disorder), demonstrated genome-wide significance at 1q42 and suggestive linkage at 22q11, with linkage evidence being contributed equally from 'schizophrenia families' (ie where other members had predominantly schizophrenia) and 'bipolar families' (ie where other members had predominantly bipolar disorder).[89]

Gene studies

Most persuasively, several recent reports implicate variation at the same loci as influencing susceptibility to both schizophrenia and bipolar disorder. Currently the best supported locus for bipolar disorder is *G72(DAOA)/G30* on chromosome 13q,[37–40] which also has positive association reported in schizophrenia.[36,39,90,91]

The *DISC1* locus at 1q42 receives linkage support in schizophrenia[92–94], bipolar disorder[95] and schizoaffective disorder,[89]and, although it has been named Disrupted in Schizophrenia, the family in which the translocation was observed contained cases of both psychosis and mood disorder.[92] Evidence for allelic association at polymorphisms at this locus has been reported for schizophrenia, bipolar disorder and schizoaffective disorder.[96]

Neuregulin 1 is one of the best supported schizophrenia susceptibility genes with several studies showing evidence that a so-called Icelandic 'core haplotype' is associated with increased risk in Icelandic, Scottish, and UK populations.[97–99] We have found that this same haplotype is significantly associated with risk for bipolar disorder and that it may exert a specific effect in the subset of functional psychosis that has both manic and mood-incongruent psychotic features.[100]

The COMT gene lies at 22q11, a region implicated in bipolar disorder and schizophrenia.[19] It is extremely likely that genetic variation in this region influences susceptibility across the psychosis spectrum (eg, Shifman *et al*[34,35]), although it is not yet clear that *COMT* itself is *the* (or the major) susceptibility gene at this locus.

These gene findings provide strong evidence that, as suggested by the family and twin data, there are genetic loci that contribute susceptibility across the Kraepelinian divide to schizophrenia, bipolar disorder and schizoaffective disorders. These findings have important implications for classification of the major psychiatric disorders because they demonstrate an overlap in the biological basis of disorders that, over the last 100 years, have been assumed to be distinct entities.[101] Molecular genetic findings are likely to catalyse a reappraisal of psychiatric nosology as well as providing a path to understanding the pathophysiology that will facilitate development of improved

treatments. Rather than classifying psychosis as a dichotomy, a more useful formulation may be to conceptualise a spectrum of clinical phenotype with susceptibility conferred by overlapping sets of genes.[101]

Conclusions

Positive findings are beginning to emerge from molecular genetic studies of mood disorders. Replications of current findings in large, well-characterised samples are required to determine their robustness and generalisability. It will be necessary to undertake detailed phenotype–genotype studies across the mood-psychosis spectrum as well as functional biological studies to determine how biological variation influences clinical phenotype. It can be expected that some current findings will prove to be false positives and there will be many more susceptibility or disease modifying genes to be identified in future studies. New methodologies including whole genome association studies can be expected to complement existing approaches to facilitate progress.

In the past, psychiatric genetics has often attracted the pessimistic view that it is an area of endeavour that is so complex that advances were unlikely. However, promising findings are now emerging and the potential benefits for the practice of clinical psychiatry should not be underestimated.[102] In addition to facilitating the development of treatments better targeted at the biochemical lesions involved in disease, it is also likely to lead to the development of a more rational aetiologically-based classification system which will provide a much better guide to treatment and prognosis than current systems. Importantly, identifying susceptibility genes will facilitate the identification of environmental factors that alter risk. Once these environmental factors are characterised, it may prove possible to provide helpful occupational, social and psychological advice to individuals at genetic risk of affective disorders. It is also likely that along this path we will learn much about the biological basis of normal affective responses.

In addition to the undoubted benefits, the potential costs must also be considered.[102] Major advances raise major ethical issues. Many of these issues are no different from those that arise in the context of other complex familial disorders, but the combination of genetics and mental illness raises particular concerns and has justifiably received close scrutiny of ethical and psychosocial issues.[103] It is important that we continue to address potential problems such as the availability of services, the right to information and the testing of individuals below the age of consent. The challenge is to translate advances in understanding of the complex aetiology of affective disorders into tangible improvements in clinical care.

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