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SPECIAL ISSUE

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Genetic models of schizophrenia and bipolar disorder

Overlapping inheritance or discrete genotypes?

Abstract Schizophrenia and affective disorder have been considered to be nosologically and etiologically distinct disorders. This postulate is challenged by progress in new biological research. Both disorders are strongly influenced by genetic factors; thus genetic research is a main contributor to this discussion. We review current evidence of the genetic relationship between schizophrenia and affective disorders, mainly bipolar disorder (the various genetic research methods have been particularly applied to bipolar disorder). Recent family and twin studies reveal a growing consistency in demonstrating cosegregation between both disorders which is difficult to detect with certainty given the low base rates. Systematic molecular genetic search for specific genes impacting on either disorder has now identified one gene which is apparently involved in both disorders (G72/G30); other candidate genes reveal some evidence to present as susceptibility genes with very modest effects for each of both disorders, although not consistently so (e. g., COMT, BDNF). There is room for speculation about other common susceptibility genes, given the overlap between candidate regions for schizophrenia and those for bipolar disorder emerging from linkage studies.

Key words schizophrenia · bipolar disorder · linkage · association · G72/G30 · psychotic bipolar disorder

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Introduction

The distinction between schizophrenia and bipolar disorder was historically based on distinct phenomenologies and long-term courses. A differential nosology and etiology was postulated, however never convincingly proven. The dichotomic postulate was maintained despite striking similarities in prevalence rates and risk factors between both "lifetime" disorders: Lifetime prevalence rates are similar (~ 1 %) and stable across countries and cultures, male-to-female ratios of affected subjects are balanced, age at onset reveals a broad overlap in the age period of 18–30 years. However, there is also evidence for differences in risk factors (Mortensen et al. 2003): e. g., premorbid IQ score presents a risk factor for schizophrenia but not so for bipolar disorder (Zammit et al. 2004).

Both disorders are under genetic control with very similar recurrence rates of 5–10 % for siblings and parents, similar concordance rates (~10 % for DZ and ≥ 50 % for MZ twins), and about 60–80 % of the variance being influenced by genetic variants in both disorders, and the remainder being due to individuum-specific environmental factors which are not shared among the twins; a monogenic, Mendelian transmission cannot be observed for either of the two disorders; both also reveal genetic-familial bonds to unipolar depression; variation of prevalence/incidence rates by season of birth seems also to be a characteristic of both disorders.

The similarity in risk factors between both disorders is now extended by neurobiological communalities: There is rapidly growing evidence that the psychopathology or/and the nosologically based disease entities are not based on distinct pathogenic processes. For example, both disorders share morphometric features, such as enlarged ventricles and reduced hippocampal volumes, neurophysiological patterns, such as reduced amplitudes of evoked potentials (as P300), and various memory dysfunctions. Recently, common cellular and molecular patterns were observed, e. g., gluta-

mate-mediated excito-toxicity in the cingulum (Woo et al. 2004). Similar patterns of gene expression in post-mortem hippocampal tissues (e. g., reduced GABA-ergic markers or neurotrophic factors as BDNF; Knable et al. 2004) pointing at similar oligodendrocyte dysfunction (Tkachev et al. 2003), or similar alterations in mRNA of receptors in crucial prefrontal and hippocampal areas pointing at similar dysfunctions in signal transduction (Lopez-Figueroa et al. 2004) are common between schizophrenia and bipolar affective disorders. Furthermore, in both disorders similar abnormalities of intracellular molecules linking different neurotransmitter systems with intracellular enzymes (like PSD95) that mediate signalling and provide links between different neurotransmitter systems were found, e. g., in key areas of the thalamus (Clinton and Meador-Woodruff 2004). These neurobiological communalities are supplemented by recent progress in genetic research.

We review the current evidence of a genetic relationship between schizophrenia and affective disorders on an epidemiological and molecular level.

Family and twin studies

For many decades familial aggregation of schizophrenia and bipolar disorder without cosegregation of both disorders was cited as a strong argument for the dichotomic position. The empirical proof of this argument requires family and twin studies covering simultaneously bipolar disorder and schizophrenia in comparison to controls. Only a very few family studies fit these criteria. The empirical evidence in favor of a nosological dichotomy of schizophrenia and bipolar disorder emerging from these studies is not in agreement with a dichotomic position. A hallmark study, the Iowa-500 study by Tsuang et al. (1980), revealed an excess of bipolar disorder in families of probands with schizophrenia. Other controlled family studies observed a link of schizophrenia as well as of bipolar disorder to unipolar depression (Gershon et al. 1988; Maier et al. 1993), or an aggregation of psychotic affective disorders in families of probands with schizophrenia and bipolar disorder (Kendler et al. 1993). More recent family reports produced an even more distinct overlap of bipolar disorders in families of schizophrenic patients and vice versa (Valles et al. 2000; Maier et al. 2002). The most recent extended study in siblings was conducted through case registers in New Zealand (Osby et al., verbal communication) reporting a relative risk (odds ratio) of 3.6 (2.9–4.4) for bipolar disorder among first-degree relatives of probands with schizophrenia, and of 4.4 (3.5–5.4) for schizophrenia among first-degree relatives of probands with bipolar disorder (comparator: unaffected controls). In comparison, the recurrence risks for schizophrenia in relatives was increased by a factor of 7.4 (6.8–8.1), and for bipolar disorder in relatives by a factor of 12.8 (10.6–15.3). Given that diagnoses were derived from registers, misclassifications cannot be excluded and possibly influenced the magnitude of reported results. However, other studies with extremely carefully validated diagnostic procedures are pointing in a qualitatively similar direction. High-risk studies in offspring of probands with schizophrenia in comparison to probands with affective disorders demonstrated excess cosegregation: more cases with psychotic disorders in kids of affective disorder probands, more cases with affective disorders in kids of schizophrenia parents compared to the general population (Erlenmeyer-Kimling et al. 1997). The reanalysis of the Maudsley twin series demonstrated that the overlap of familial vulnerabilities is due to genetic factors shared between schizophrenia and mania (Cardno et al. 2002): diagnosis-specific additive genetic variance was reported as 33 % for schizophrenia, and as 19 % for mania, compared to 49 % and 68 % respectively of common additive genetic variance.

There is also symptomatic overlap between bipolar disorder and schizophrenia: psychotic affective disorders share both symptom clusters. It might be suggested that this symptomatic subgroup combines the two disorders and carries the genetic vulnerabilities to each of them. Thus, clustering of psychotic symptoms in families of patients with psychotic affective symptoms have to be explored. This possibility might at least partly explain excess risk for schizophrenia in relatives of bipolar probands; the empirical evidence for this constellation, however, is controversial (Tsuang et al. 2004).

Furthermore, aggregation of bipolar disorder in families of schizophrenic patients could be restricted to psychotic bipolar disorder which might put psychotic bipolar disorder in a distinct nosological position. Empirical evidence for these possibilities is available (e. g., Kendler et al. 1993; Maier et al. 2002) but not consistently so.

Despite this inconsistency, there is now growing evidence of a cosegregation between affective disorders (including bipolar disorder) and schizophrenia.

Search strategies for disposition genes

Both schizophrenia and bipolar disorder are genetically complex diseases driven by genetic as well as environmental factors. The search of disposition genes can be accomplished by linkage and association studies: Linkage studies identify candidate regions which are likely to host disposition genes. Candidate regions might cover broad areas on the genome (10–30 cMorgans corresponding to 10–30 million base pairs).

Association studies identify smaller regions with markers in linkage disequilibrium including those for disposition genes. Linkage disequilibrium describes dependency between the distribution of two genetic markers on the same chromosome; it is dependent on the sampled population and ranges up to 100,000 base pairs in the mean in Caucasian populations, however, meaningful genetic analyses assume linkage disequilibrium of 15,000 (Schulze et al. 2004). Thus, the associated

marker is not necessarily the directly influential variant; the marker is, however, in linkage disequilibrium with the pathogenic mutation. Association studies can be performed only with preselected specific candidate genes or can be performed across limited regions on a chromosome; genome-wide association studies require high through-put technologies with a very high number of markers (> 1 million) and are currently not feasible. Given the high risk for false positives, replication of postulated linkage and association findings are obligatory for their validity.

Currently, there are confirmed linkages between schizophrenia and markers in specific candidate regions and confirmed association findings in some candidate regions; some of them were also found to be linked to bipolar disorder. We are exploring the possibility of genetic variants which exert pleitropic effects by influencing both schizophrenia and bipolar disorder. How can linkage and association studies contribute to the clarification of this possibility? Is the overlap between candidate regions for bipolar disorder and for schizophrenia informative to this question? Is the association of a marker to schizophrenia as well as to bipolar disorder able to provide evidence for common genetic determinants?

Linkage analyses

Genome-wide linkage analysis is a very efficient tool in detecting causal disease genes in monogenic disorders. This technique is less efficient in genetically influenced complex diseases with multiple contributing genes. Initially, a high degree of inconsistency was noted among implicated candidate regions in about 20 schizophrenia and about 18 bipolar disorder scans, and the appropriateness of this strategy for genetically complex disorders was critically discussed (DeLisi et al. 2002). Most investigated samples, however, were underpowered to be able to replicate postulated linkages to candidate regions. Meta-analyses combining all published genome-wide scans provide a feasible opportunity to circumvent this limitation.

Two meta-analyses were performed for schizophrenia as well as for bipolar disorder; fortunately, the data analysis was performed in parallel for schizophrenia and bipolar disorder allowing conclusions on the overlap of candidate regions. Overall, both metaanalyses conclude that there is substantially more consistency than expected on the basis of a comparison between suggestive linkage results of specific linkage studies. However, the analytic technique for a metaanalysis of linkage studies is not straightforward: Given the variation of linkage disequilibrium between nearby markers across populations the positional information of a linkage signal is not accurate. We have two sources of evidence for linkage on the basis of multiple studies: (a) the actual linkage scores combined across various studies at a specific marker locus, and (b) the aggregation of linkage signals in a small region with multiple markers in linkage disequilibrium. The various techniques of meta-analyses give differential weight to these alternative rationales resulting in different candidate regions. Yet, as both modes of reasoning are appropriate, all metaanalytic conclusions based on different analytic techniques might be true. Yet, two different analytic methods were applied resulting in different confirmed linkage findings:

Badner and Gershon (2002) used only a subset of published genome scans and found strong evidence for linkage:

- For schizophrenia on 13q31 and 22q11–13, with the 13q-linkage showing strongest evidence ($p < 6 \times 10^{-6}$),
- For bipolar disorder on 8p22, 13q31 and 22q11–13, with the 13q-linkage showing the maximal evidence ($p < 7 \times 10^{-5}$).

Thus, most of the identified candidate regions (22q and 13q) with strongest evidence (i. e., genome-wide statistical significance) reveal an overlap between the two disorders.

The more comprehensive meta-analyses by Lewis et al. (2003) for schizophrenia and by Segurado et al. (2003) for bipolar disorder found strong evidence for linkage only for schizophrenia; evidence for linkage to bipolar disorder was only moderate. Ignoring this difference the strong and/or moderate evidence for linkage was found in the following chromosomal regions:

- For schizophrenia primarily on 2q, but also on 5q, 3p, 11q, 6p, 1q, 22q, 8p, 20q and 14p,
- For bipolar disorder on 10q11.21–22, 9p22–21, 14q24–32.

Thus, just considering the strongest p-values for candidate regions no overlap of candidate regions between schizophrenia and bipolar disorder can be concluded according to this more comprehensive analyses. Yet, there is still a considerable number of overlapping candidate regions if nominal p-values ($P_{AvgRnk} < 0.05$) are also considered:

- 2q22.1-q23.3 for both disorders,
- 8p22 (8pter-p22 for bipolar disorder, and 8p22-p21.1 for schizophrenia),
- 14q13.1 (14q13.1-q24.1 for bipolar disorder, and 14pter-14q31.1 for schizophrenia).

These are three overlapping candidate regions among 12 candidate regions for schizophrenia and 21 candidate regions for bipolar disorder with nominally significant p-values.

Previously, a systematic review of the published genome scans exploring regions of overlap between replicated diagnosis-specific candidate regions proposed five common linked regions (Berrettini 2003): 18p11.2, 13q32, 22q11–13, 8p22, 10p14.

Thus, although the combined analysis of available genome-wide linkage analyses provided different re-

sults depending on the applied method, a considerable overlap of validated candidate regions between schizophrenia and bipolar disorder can be observed – for all modes of biometric analyses.

Pleiotropic genetic effects with a specific DNA-sequence variation influencing the manifestation of two different disorders can only be proven if the pathogenic mutation is known. Linkage to the same candidate region and association to the same marker can only propose the possibility of common genetic determinants.

Cytogenetic abnormalities

Several defined cytogenetic alterations of the DNA string reveal major psychiatric syndromes. Most extensively explored are a translocation on chromosome 1q and chromosome 22q microdeletions. It is most noteworthy that both abnormalities are associated with the occurrence of schizophrenia as well as of affective disorders in the same families.

A balanced reciprocal translocation (1; 11) (q42; q14.3) was found to cosegregate with psychotic syndromes in a large Scottish family (Blackwood et al. 2001). Strong linkage at this region q42 was calculated for schizophrenia (LOD score = 3.6), and even higher for affective disorders (LOD score = 4.5); linkage can be maximized by considering all kinds of psychotic and affective disorders as affected (LOD score = 7.1). A refined clinical analysis revealed that the DISC phenotype includes schizophrenia, schizoaffective disorder, bipolar disorder and recurrent major depression but also neurophysiological abnormalities in the absence of clinical diagnoses; particularly, the most common abnormality among carriers of the balanced t (1; 11) translocation shows a reduced P300 amplitude in response to an oddball discrimination task which occurred in carriers with the various mentioned diagnoses as well as in unaffected carriers (Blackwood and Muir 2004). This neurophysiological abnormality is also consistently observed in schizophrenia but also in affective disorders (Friedman and Squires-Wheeler 1994; Pierson et al. 2000).

The translocation disrupts two genes which were called DISC1 and DISC2; they might be involved in the cytoskeletal regulation which is relevant for neuronal development, neuronal architecture and intracellular transport. In particular DISC1 interacts with a variety of cytoskeletal proteins, some of them are associated with cortical development (Ozeki et al. 2003). The translocation has up to now only been observed in a single family. Could the family-specific linkage be of more general relevance? The answer is yes, as the translocated 1q region is closely located to markers showing linkage to schizophrenia in two Finnish samples (Hovatta et al. 1999; Ekelund et al. 2001). Thus, the DISC1 and DISC2 genes are hot candidates for susceptibility genes of major disorders. Yet, the pathogenic mutations still have to be identified.

The Velo-Cardio-Facial syndrome (VCFS) – also called DiGeorge syndrome – is a monogenic disorder caused by interstitial deletions in a specific region of chromosome 22: q11. This syndrome is characterized by facial malformations and congenital heart disease. It reveals a sharp excess of prevalence in major psychiatric syndromes of more than 25 % (Bassett et al. 2001) – mainly with severe psychotic and affective disorders which are similar to both schizophrenia and bipolar disorder (Carlson et al. 1997). These disorders are also segregating and cosegregating in the VCFS families.

Given the very small prevalence (< 1‰) of VCFS in the general population, the impact of this syndrome-specific genetic association on schizophrenia as well as on bipolar affective disorders might be negligible. Yet, the 22q11 microdeletions are also slightly more common in unselected samples of patients with schizophrenia (2 % compared to 1 % among 4000 in the general population) (Scambler 2000); similar figures for bipolar disorder are not available. Although linkage of schizophrenia to 22q11 did not show up in a recent large-scale multicenter study (Mowry et al. 2004), it has been revealed to be one of the most consistent and strongest findings emerging in another meta-analysis covering all published genome-wide scans (Badner and Gershon 2002). Thus, it is possible that the same gene in 22q11-q22 is impacting on schizophrenia and bipolar disorder in the VCFS families as well as in larger samples of multiplex families. There is considerable dispute about which of the genes in the 22q11 region presents as a disposition gene; e. g., there is some but still insufficient evidence for COMT (Shifman et al. 2002) and PRODH2 (Liu et al. 2002) in schizophrenia; the COMT gene is also discussed as a disposition gene for bipolar disorder (Shifman et al. 2004) (s. below).

Susceptibility genes

There is rapidly growing evidence for DNA-sequence variations in specific genes to be implicated in the manifestation of schizophrenia. A substantial proportion of these genes are apparently also involved in the etiology of bipolar disorder. Currently, it is quite evident that the neuregulin-1 gene, dysbindin gene, G72/G30 gene and possibly also the COMT gene are involved in schizophrenia (Chumakov et al. 2002; Shifman et al. 2002; Straub et al. 2002; Schwab et al. 2003a; Stefansson et al. 2002, 2003). Subsequently, it was recognized that the G72/G30 gene and possibly also the COMT gene are also involved in the etiology of bipolar disorder evidenced by identical markers for both disorders (Hattori et al. 2003; Schumacher et al. 2004).

Complex behaviors, such as psychotic and affective disorders, are influenced by multiple genes, and an influencing gene generally affects multiple behavioral components at various physiological functions (Kas and van Ree 2004). In this context it is of interest that each of the identified genes is involved in multiple physiological pathways; simultaneously, the physiological targets are,

however, very similar between the identified susceptibility genes (with the exception of the COMT gene): they are involved in the glutamatergic transmission (Collier and Li 2003) and in the development and the survival of neurons and glia cells. However, the functional consequences of each of these genes are currently only poorly understood.

G72/G30 gene

The strongest support for specific susceptibility genes common to schizophrenia and bipolar disorder comes from the G72/G30 gene in the 13q candidate region (Hattori et al. 2003; Addington et al. 2004; Chen et al. 2004; Korostishevsky et al. 2004; Wang et al. 2004). There is a curiosity with this gene locus: G30 and G72 are two overlapping genes with G30 including G72; the over-transmitted marker variants and haplotypes differ between populations (Korostishevsky et al. 2004). A haplotype in this gene was found to be associated with schizophrenia in a Russian and a Canadian sample, and was subsequently replicated in several other samples including a German sample (Chumakov et al. 2002; Schumacher et al. 2004). Associations of other G72/G30 haplotypes were also reported for schizophrenia in the Ashkenazi population (Korostishevsky et al. 2004) and for childhood-onset schizophrenia (Addington et al. 2004). The pathogenic mutations have not yet been identified but might be located in the vicinity of this gene complex or in the regulatory region (Korostishevsky et al. 2004).

The overlap of the candidate regions in this chromosomal section between schizophrenia and bipolar disorder motivated the genetic association studies in bipolar disorder with the identical G30 haplotype being found to be associated with bipolar disorder and schizophrenia. However, in some populations the at-risk haplotypes are shared between schizophrenia and bipolar disorder (Schumacher et al. 2004). The function of both genes is not yet known. However, G30 is in vitro interacting with the DAOA gene (D-amino-acid oxidase activator); genetic variants of this gene were also found to be associated with bipolar disorder and schizophrenia (Schumacher et al. 2004) but not consistently so (Hattori et al. 2003). DAOA is of particular interest as it degrades serine which modulates the glutamatergic NMDAR1 receptor that is differently expressed in both disorders, schizophrenia and bipolar disorder (Law and Deakin 2001).

Leboyer et al. (1998) discussed the possibility that the more basic symptoms might be more strongly related to susceptibility genes than those symptom patterns which are defining disorders which are validated through clinical conventions. They proposed the concept of candidate symptoms; a refined phenotype analysis by Schulze et al. (in press) applied this idea and searched for symptoms with a strong relationship to the G30 at-risk haplotype among subjects with bipolar disorder. Persecutory delusions were the only symptom with this property; this finding is unlikely to be a false positive as it could be replicated in an independent sample. As a consequence a distinct etiological status of bipolar disorder with this specific psychotic symptom can be concluded.

BDNF gene

The brain-derived neurotrophic factor (BDNF), the gene being located on chromosome 11p13 outside of confirmed candidate regions, belongs to the family of neurotrophic factors and is involved in neuronal development, migration, growth and survival of neurons, but also in active-dependent neuronal activity and learning processes as long-term potentiation (Green and Craddock 2003). BDNF transcripts are reduced in the hippocampus of both bipolar disorder and schizophrenia (Knable et al. 2004). The gene is expressed in hippocampus and neocortex, and reveals several polymorphisms; one of them results in an amino-acid substitution with functional impact in cell models on activity-dependent secretion (Val66Met); the more common variant of this polymorphism is also associated with enhanced episodic memory achievement (Egan et al. 2003). Two other polymorphisms in nonexpressed sections of the gene are also known. Thus, the BDNF gene presents as an a-priori ideal candidate gene for both bipolar disorder and schizophrenia. And indeed, two convincing family-based association studies proposed an association of the common Val-variant with bipolar disorder in Caucasian populations (Neves-Pereira et al. 2002; Sklar et al. 2002) which could, however, not be replicated in Japanese populations (Nakata et al. 2003).

An unexpressed dinucleotide repeat $(GT)_n$ polymorphism located close to the promoter region of the BDNF gene was also reported to be associated with schizophrenia in one but not in several other samples (Muglia et al. 2003). Furthermore, in a single study another polymorphism using a novel nucleotide substitution (C270T) was investigated in a recent case-control sample with cases having schizophrenia, and provided a positive result (Szekeres et al. 2003).

Taken together, the positive association results with multiple polymorphisms are difficult to interpret in the context of negative reports both for schizophrenia and bipolar disorder. The BDNF gene, thus, remains a very promising candidate gene which might have a modest effect on each of the two disorders.

COMT gene

The catechol-O-methyltransferase (COMT) gene is located in the 22q11 candidate region for schizophrenia and bipolar disorder which is confirmed in meta-analysis. The gene product is a dopamine-degrading enzyme; dopamine is involved in the pathophysiology of schizo-

phrenia and bipolar disorder. The COMT gene carries multiple polymorphisms where at least one of them is of functional relevance: Val158Met. The Met-variant causes substantially reduced enzyme activity inducing increased levels of dopamine in the prefrontal area which is involved in working memory (which is impaired in schizophrenia as well as in bipolar disorder); consequently, carriers of this more common Val-variant are less efficient in working memory tasks independent of their affection status (Egan et al. 2001). The Val-variant was also proposed to be over-transmitted in subjects with schizophrenia, but up to now the cumulative evidence is only spurious with maximally a very small effect size (Glatt et al. 2003). However, haplotypes tapping three other polymorphisms turned out to be more strongly associated with schizophrenia (Shifman et al. 2002). The same haplotype turned out to be also associated with bipolar disorder (Shifman et al. 2004). Thus, the COMT or another nearby gene is likely to be involved in one or both disorders, but the functional Val158Met variant is probably not of pathogenic impact.

PIPK2A gene

A most interesting candidate region in this context is 10p12. Linkage to schizophrenia has been confirmed in several family studies (Faraone et al. 1998; Schwab et al. 1998; Foroud et al. 2000). Linkage to bipolar disorder was also reported (Rice et al. 1997). These linkage results are complemented by associations to a variant of the PIP5K2A gene, in both schizophrenia and bipolar disorder (Stopkova et al. 2003). Schwab et al. (1998) also detected variants of the closely nearby placed PIPK2 gene for schizophrenia. Remarkably, both genes are involved in the phosphate inositol metabolism. Phosphoinositol pathways are involved in intracellular signal transmission, particularly in the context of long-term potentiation, a mechanism relevant for episodic memory which is impaired in schizophrenia; furthermore, phosphoinositol is modulated by lithium. It is speculated that an inositol deficit contributes to bipolar disorder. The phosphoinositol-related findings might introduce a hypothetical common neurobiological basis for schizophrenic and manic syndromes with therapeutic implications. Yet, the implication of phosphoinositol-related genes still has to be confirmed. In this context it is particularly relevant to notice that PIP5K2A is a critical component of the phosphoinositide and inositol phosphate pathways which are modulated by lithium, an effective drug for bipolar and schizoaffective disorders.

Other candidate genes can also be discussed as being related to schizophrenia as well as to bipolar disorder, particularly DNA-sequence variants in genes coding for proinflammatory factors: the interleukin-1β in the interleukin-1 cluster on chromosome 2q13 (outside of the candidate region 2q22) (Papiol et al. 2004), and the tumor necrosis factor alpha gene located in the schizophrenia candidate region 6p close to the HLA region (Schwab et al. 2003b; Pae et al. 2004); the empirical basis, however, is limited and far from being convincing. Further replications are required.

Conclusion

There is emerging evidence that schizophrenia and bipolar disorder define no etiologically distinct disorders. A series of family and twin studies as well as molecular-genetic studies propose some etiological overlap which is at least partially due to genetic factors. In conclusion there is overlapping inheritance which might be due to shared polygenic mutations in the same disposition genes in terms of cosegregation in families and twins.

A first common disposition gene (G72/G30) was identified for both disorders, and it can be expected that other disposition genes of this kind will follow given the overlap of candidate regions detected by linkage analysis and common functional and molecular neurobiological features, although some association studies observed the same at-risk haplotype associated with both disorders. As the pathogenic variants have not yet been identified it still remains unclear if both disorders are driven by the identical genetic variants and mechanisms (e. g., in the gene G72/G30). Given the strong DNA-sequence variability observable in many genes, two closely located but different variants within the same gene coding specifically for each of both disorders remain a possibility.

Diagnostic entities are based on clinical conventions which might lack etiological and pathophysiological validity. Therefore, the observed genetic overlap between schizophrenia and bipolar disorder might have different meanings. The most plausible alternatives are:

- Both or one of the disorders are etiologically and pathophysiologically heterogeneous, e. g., there is a distinct subtype (e. g., psychotic bipolar disorder) explaining the overlap but not being considered as a separate diagnostic entity.
- Both disorders share common symptomatic and or neurophysiological features which have their own genetic underpinning which is consequently shared between both disorders.
- Complex behavior is driven by multiple genes, and each variant in these genes predisposes to different aspects of behavior depending on spatial distribution of gene-expression patterns which might be triggered by environment (pleiotropy); thus, the same genetic factor might induce schizophrenia as well as bipolar symptoms depending on the context.

Although some arguments were discussed in favor of the second possibility, the current status of knowledge does not allow a conclusive decision.

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