Clinical and Molecular Genetics of Psychotic Depression

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This review provides a comprehensive overview of clinical and molecular genetic as well as pharmacogenetic studies regarding the clinical phenotype of “psychotic depression.” Results are discussed with regard to the long-standing debate on categorical vs dimensional disease models of affective and psychotic disorders on a continuum from unipolar depression over bipolar disorder and schizoaffective disorder to schizophrenia. Clinical genetic studies suggest a familial aggregation and a considerable heritability (39%) of psychotic depression partly shared with schizoaffective disorder, schizophrenia, and affective disorders. Molecular genetic studies point to potential risk loci of psychotic depression shared with schizoaffective disorder (1q42, 22q11, 19p13), depression, bipolar disorder, and schizophrenia (6p, 8p22, 10p13-12, 10p14, 13q13-14, 13q32, 18p, 22q11-13) and several vulnerability genes possibly contributing to an increased risk of psychotic symptoms in depression (eg, BDNF, DBH, DTNBP1, DRD2, DRD4, GSK-3beta, MAO-A). Pharmacogenetic studies implicate 5-HTT, TPH1, and DTNBP1 gene variation in the mediation of antidepressant treatment response in psychotic depression. Genetic factors are suggested to contribute to the disease risk of psychotic depression in partial overlap with disorders along the affective-psychotic spectrum. Thus, genetic research focusing on psychotic depression might inspire a more dimensional, neurobiologically and symptom-oriented taxonomy of affective and psychotic disorders challenging the dichotomous Kraepelinian view. Additionally, pharmacogenetic studies might aid in the development of a more personalized treatment of psychotic depression with an individually tailored antidepressive/antipsychotic pharmacotherapy according to genotype.

Key words: twin studies/family studies/linkage studies/association studies/pharmacogenetics

Major depression is a complex-genetic disorder with a 2 to 3-times increased risk of depression in first-degree relatives and a considerable heritability of ~40%. However, the majority of molecular genetic and pharmacogenetic findings in major depression lack or still warrant positive replication in independent samples. This problem of not unequivocally identifiable genetic risk variants in complex-genetic disorders such as major depression might be due to underpowered, relatively small samples, ethnic stratification, differences in mean age or comorbidities with either mental or somatic disorders across different studies. Another major reason for non-replication of genetic findings in major depression might be the heterogeneity of the clinical phenotype captured by “major depression” across different studies and across different individual patients enrolled in those studies. Rather, clinical subtypes of major depression might constitute separate nosological entities with a specific genetic risk profile, also with respect to antidepressant treatment response.

Along the search for a more biologically grounded depressive typology, besides melancholic or anxious depression the subtype of psychotic depression affecting about 20% of depressed patients has been suggested as a nosological entity of its own, characterized by feelings of worthlessness or guilt, delusions, or hallucinations as well as a more severe course, an increased risk of relapse, a higher socioeconomic burden, and an overall worse outcome. This clinical subtype of depression is of particular relevance on the background of the longstanding debate about the Kraepelinian dichotomy of psychotic disorders on the one hand and affective disorders on the other hand, which to a certain degree seems to be dissolved in the phenotype of “psychotic depression.” Accordingly, increasing research attention is paid to the genetic pathomechanism of “psychotic mood disorders,” which is hoped to aid in re-evaluating the proposed nosological dichotomization by unravelling the neurobiological underpinnings of psychotic depression placed on a continuum between schizophrenia, schizoaffective disorders, and affective disorders.
This review is dedicated to providing a comprehensive overview of presently available clinical and molecular genetic as well as pharmacogenetic studies regarding psychotic depression and to discussing the results with regard to the ongoing debate on categorical vs dimensional disease models of affective and psychotic disorders along the depression/bipolar/schizoaffective/schizophrenia spectrum.

Clinical Genetics

Family Studies

One of the first family studies explicitly investigating the clinical phenotype of psychotic/delusional depression discerned an aggregation of both schizophrenia and affective disorders in families of depressed patients with “schizophrenic or paranoid symptoms.” Later, Leckman et al. identified the highest rate of major depression in relatives of patients with “depression of the delusional subtype” compared with patients with other subtypes of depression (“endogenous,” “melancholic”). This finding was replicated in several independent studies suggesting a familial aggregation of psychotic depression: In relatives of patients with delusional depression compared with nondelusional depression, an increased risk of particularly psychotic major depression was reported. Coryell and Zimmerman also discerned an increased risk of affective disorders particularly in patients with psychotically depressed patients, and Goldstein et al. investigating first-degree relatives of patients with major depression reported relatives of patients with delusional depression to be at a higher risk for depression compared with first-degree relatives of patients with nondelusional depression. Endicott et al. explicitly observed a higher risk of psychotic major depression in families of probands with major depressive disorder of the psychotic subtype. A particular familial aggregation has furthermore been shown for depression with mood-incongruent (delusions or hallucinations not relating to guilt, inadequacy, responsibility, punishment, disease, finances, or death) compared with mood-congruent (delusions or hallucinations relating to guilt, inadequacy, responsibility, punishment, disease, finances, or death) psychotic features. In a study focusing on bipolar disorder, Weissman et al. identified a nearly 6 times higher risk of bipolar disorder relatives of patients with delusional depression than in nondelusional depressed patients, which could be corroborated by several studies observing an increased familial risk of bipolar disorder particularly in the presence of psychotic major depression. In contrast, a study by Coryell et al. did not yield differences in the prevalence of affective disorders (12.8% vs 13.3%) or schizophrenia (0.8% vs 0.2%) in families of patients with delusional vs nondelusional unipolar depression. Also, Price et al. failed to discern differential rates of affective (14.1% vs 13.6%) or psychotic (0.5% vs 1.9%) illnesses in families of patients with delusional vs nondelusional depression, and Winokur et al. did not observe differences in psychotic symptoms in relatives of patients with psychotic vs nonpsychotic affective disorders.

Results from family study on the familial aggregation of schizoaffective disorder and its relation to schizophrenia and bipolar disorder are controversial: While Gershon et al. report the highest risk of affective disorders including schizoaffective disorder in relatives of probands with schizoaffective disorder compared with patients with bipolar I, bipolar II, and unipolar depressive disorder, other family studies in schizoaffective disorder did not corroborate a particular familiality of the disorder. Other studies provided evidence for schizoaffective disorder to increase the risk for both affective disorders and schizophrenic spectrum disorders, with some support for a potentially sex-based heterogeneity as female relatives of patients with schizoaffective disorder have been observed to display a higher risk of affective disorders than males, while the risk for schizophrenia was equally high in female and male relatives of patients with schizoaffective disorder.

Family studies also demonstrate a mutual co-occurrence of schizophrenia and affective disorders in families (for review, see Maier et al. and Taylor): eg, in a sample of patients with a first episode of psychosis, 53.2% of the patients had a first-degree relative with major depression, and in patients with nonaffective psychosis and their siblings the number of depressive symptoms was found to be associated with (sub)clinical positive symptoms in the Genetic Risk and Outcome of Psychosis study. Reciprocally, an increased risk of schizophrenia was discerned in first-degree relatives of patients with affective disorders.

Twin and Adoption Studies

Some twin studies have explicitly analyzed the influence of genetic factors on the pathogenesis of psychotic depression or a possible genetic overlap between affective and psychotic disorders, respectively: In the Vietnam Era Twin Registry sample, the subtype of severe and particularly psychotic major depression was found to be significantly affected by genetic factors with a heritability of 39%. In the Maudsley Twin Register sample, schizoaffective depression was reported to be due to co-occurring elevated liability to schizophrenia and depression, and a considerable overlap of heritabilities for schizophrenia, schizoaffective disorder, and mania was demonstrated. In a study of twins discordant for schizophrenia, nonschizophrenic co-twins displayed significantly increased rates of depression compared with the control twins, which, however, could not be observed in a similarly designed study. Also, two publications emerging from the Danish Adoption Study of Schizophrenia do not support a significant genetic
relationship between schizophrenia spectrum disorders and major depression.\textsuperscript{36,37}

In synopsis of all clinical genetic studies reviewed above, despite some inconsistencies, a familial aggregation and a considerable heritability of psychotic depression partly shared with schizoaffective disorder as well as both affective and psychotic disorders suggest overlapping genetic factors to contribute to the disease risk along this diagnostic spectrum.

**Molecular Genetics**

**Linkage Studies**

Although to the best of our knowledge no linkage study explicitly distinguished between the clinical phenotypes of psychotic and nonpsychotic depression, indirect support for possible risk loci of psychotic depression can be deduced from linkage studies in schizoaffective disorder (risk loci on chromosomes 1q42, 22q11, and 19p13)\textsuperscript{38} as well as from linkage studies reporting an overlap between risk loci for depression, bipolar disorder, schizophrenia, and schizoaffective disorders on chromosomes 6p, 8p22, 10p13-12, 10p14, 13q13-14, 13q32, 18p and 22q11-13 (see Wildenauer et al.\textsuperscript{39}, Gershon and Badner\textsuperscript{40}, and Maziaede et al.\textsuperscript{41}).

**Association Studies**

Several molecular genetic association studies have focused on the identification of genetic variants, which increase the risk of specifically psychotic symptoms in major depression (see table 1): In a Japanese sample of patients with major depression, the met allele of the brain derived neurotrophic factor (BDNF) val66met polymorphism was found to be associated with particularly psychotic features.\textsuperscript{42} Domschke et al. discerned several single nucleotide polymorphisms in the dysbindin (DTNBPI) gene to be associated with psychotic compared with nonpsychotic major depression,\textsuperscript{43} which is in accordance with the hypothesis of dysbindin crucially influencing dopamine and glutamate neurotransmission as relevant for psychotic disorders.\textsuperscript{44} Paranoid ideation in patients with major depression has been observed to be influenced by the A allele of the exonic 444G/A variant in the dopamine beta-hydroxylase (DBH) gene.\textsuperscript{45} This finding is supported by a report of lower DBH plasma levels in patients with psychotic depression compared patients with nonpsychotic depression, which was hypothesized to be due to a dysfunctional regulation of the hypothalamic-pituitary-adrenal axis in psychotic depression.\textsuperscript{46} Some evidence has furthermore been reported for the more active allele of the monoamine oxidase A (MAO-A) variable number of tandem repeats (VNTR) to be associated with psychotic features in major depression, particularly in female patients,\textsuperscript{47} which is consistent with higher platelet MAO activity in patients with psychotic vs nonpsychotic depression.\textsuperscript{48} In a sample of patients with both major depression and bipolar disorder, Serretti et al. observed association of the -50T/C polymorphism in the glycogen synthase kinase 3beta (GSK-3beta) gene with delusional symptoms, with some evidence for an interactive effect of GSK-3beta gene variation and personality features linked to self-transcendence.\textsuperscript{49} Several other molecular genetic association studies in affective disorders have explicitly controlled for psychotic features as assessed by the Operational Criteria Checklist for Psychotic Illness (OPCRIT) and have excluded association of serotonin transporter (5-HTT), serotonin receptor 1A (HTR1A), serotonin receptor 2A (HTR2A), serotonin receptor 2C (HTR2C), and tyrosine hydroxylase (TH) gene variation with psychotic features of depression\textsuperscript{50-53} (see table 1).

Reciprocally, several association studies have investigated the genetic underpinnings of depressive symptoms in psychotic disorders: Rinetti et al. reported association of the dopamine D4 receptor (DRD4) VNTR region with particularly affective symptoms in patients with a first psychotic episode.\textsuperscript{54} A recent association study implicated the RS3HDML and C20orf39 genes on chromosome 20 to be associated with depressed symptoms in schizophrenia,\textsuperscript{55} and the short allele of the serotonin transporter 5-HTTLPR variant was found to increase the risk of lifetime depression in patients with chronic psychotic disorders.\textsuperscript{56} Also, variation in the glycoprotein M6 (GPM6A) and the interleukin-1beta (IL-1beta) genes has been reported to be associated with the subtype of schizophrenia with high levels of depressive symptoms.\textsuperscript{57,58}

A recent cross-disorder genome-wide association study (GWAS) of schizophrenia, bipolar disorder and depression based on the CATIE, STEP-BD, and STAR*D samples revealed pleiotropic effects of neuronal PAS domain 3 (NPAS3) gene variants across all three disease entities, suggesting shared genetic influence on both psychotic and mood disorders and thus potentially psychotic depression in particular.\textsuperscript{59} Also applying a cross-disorder approach, Serretti et al. reported variation in exon 3 of the dopamine receptor 4 (DRD4) gene to be associated with delusional symptoms as assessed by the OPCRIT across major depression, schizophrenia, delusional disorder, and psychotic disorder not otherwise specified.\textsuperscript{60,61} with no evidence for a moderating influence of gamma-aminobutyric acid type A (GABA-A) gene variation on this effect.\textsuperscript{52} Association of DRD4 gene variation across affective and psychotic disorders has been corroborated in an independent sample comprising patients with schizophrenia, schizoaffective and unipolar affective disorders.\textsuperscript{63} Additionally, the dopamine receptor 2 (DRD2) S311C variant has been observed to be associated with delusional symptoms across major depression, schizophrenia, delusional disorder and psychotic disorder not otherwise specified.\textsuperscript{64} The finding of dysbindin (DTNBPI) gene variation to be associated with particularly psychotic depression\textsuperscript{43} is corroborated...
Table 1. Molecular Genetic Association Studies in Psychotic Depression

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study Population</th>
<th>Sample Size</th>
<th>Gene</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iga et al.(^{42})</td>
<td>2007</td>
<td>Japanese patients with MDD</td>
<td>N=154 (psychotic symptoms: 11%)</td>
<td>Brain derived neurotrophic factor</td>
<td>Association of met allele of val66met polymorphism (rs6265) with psychotic features ((P &lt; .001))</td>
</tr>
<tr>
<td>Domschke et al.(^{41})</td>
<td>2011</td>
<td>Caucasian inpatients with MDD</td>
<td>N=243 (psychotic symptoms: 54%)</td>
<td>Dysbindin</td>
<td>Association of rs1997679 CC genotype ((P = .015)) / rs4236167 TT genotype ((P = .009)) / rs7758659 CC genotype ((P = .02)) / rs9370822 CC genotype ((P = .01)) with psychotic depression</td>
</tr>
<tr>
<td>Wood et al.(^{45})</td>
<td>2002</td>
<td>Outpatients with MDD</td>
<td>N=164</td>
<td>Dopamine beta-hydroxylase</td>
<td>Association of A allele of exon 2 444G/A variant (rs1108580) with interpersonal sensitivity ((P = .004)) and paranoid ideation ((P = .048))</td>
</tr>
<tr>
<td>Serretti et al.(^{40})</td>
<td>2008</td>
<td>Caucasian inpatients with affective disorders; delusional symptoms verified by OPCRIT</td>
<td>N=365 (MDD: N=122, bipolar disorder: N=243)</td>
<td>Glycogen synthase kinase 3beta</td>
<td>Association of CC genotype of -50T/C promoter polymorphism (rs334558) with delusional symptoms ((P = .008))</td>
</tr>
<tr>
<td>Gutierrez et al.(^{47})</td>
<td>2004</td>
<td>Hispanic patients with affective disorders</td>
<td>N=389 (MDD: N=301 (psychotic symptoms: 25%), bipolar disorder: N=88 (psychotic symptoms: 64%))</td>
<td>Monoamine oxidase A</td>
<td>Trend for association of longer, more active alleles of uVNTR with psychotic symptoms, particularly in females ((P = .07))</td>
</tr>
<tr>
<td>Serretti et al.(^{32})</td>
<td>1999</td>
<td>Caucasian inpatients with affective disorders; delusional symptoms verified by OPCRIT</td>
<td>N=84 (MDD: N=70, bipolar disorder: N=160)</td>
<td>Serotonin transporter</td>
<td>No association of 5-HTTLPR with “delusion” factor</td>
</tr>
<tr>
<td>Serretti et al.(^{36})</td>
<td>2000</td>
<td>Caucasian inpatients with affective disorders; delusional symptoms verified by OPCRIT</td>
<td>N=84 (MDD: N=12, bipolar disorder: N=72)</td>
<td>Serotonin transporter 1A</td>
<td>No association of Ile28Val polymorphism (rs1799921) with “delusion” factor</td>
</tr>
<tr>
<td>Serretti et al.(^{36})</td>
<td>1999</td>
<td>Caucasian inpatients with affective disorders; delusional symptoms verified by OPCRIT</td>
<td>N=246 (MDD: N=97, bipolar disorder: N=149)</td>
<td>Serotonin transporter 2A</td>
<td>No association of T102C polymorphism (rs6313) with “delusion” factor</td>
</tr>
<tr>
<td>Serretti et al.(^{36})</td>
<td>2000</td>
<td>Caucasian inpatients with affective disorders; delusional symptoms verified by OPCRIT</td>
<td>N=84 (MDD: N=12, bipolar disorder: N=72)</td>
<td>Serotonin transporter 2C</td>
<td>No association of the Cys23Ser polymorphism (rs6318) with “delusion” factor</td>
</tr>
<tr>
<td>Serretti et al.(^{33})</td>
<td>1998</td>
<td>Caucasian inpatients with affective disorders; delusional symptoms verified by OPCRIT</td>
<td>N=46 (MDD: N=5, bipolar disorder: N=41)</td>
<td>Tyrosine hydroxylase</td>
<td>No association of intron 1 VNTR with “delusion” factor</td>
</tr>
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</table>

Note: MDD = major depressive disorder; OPCRIT = Operational Criteria Checklist for Psychotic Illness; VNTR = variable number of tandem repeats.
by DTNBP1 gene variation having been reported to confer an increased risk of schizophrenia (eg, Straub et al.\textsuperscript{85}, Pae et al.\textsuperscript{86}, Schwab et al.\textsuperscript{67}, van den Oord et al.\textsuperscript{68}, Fanous et al.\textsuperscript{69}, and Zuo et al.\textsuperscript{70}; for review, see Benson et al.\textsuperscript{71}), psychotic symptoms in general,\textsuperscript{72} bipolar disorder,\textsuperscript{73–77} and unipolar depression.\textsuperscript{78} Also, COMT,\textsuperscript{79} CACNA1C,\textsuperscript{80} G72(DAOA)/G30,\textsuperscript{81,82} HTR5A\textsuperscript{83} and DISC1\textsuperscript{84} have been identified as common vulnerability genes for both affective disorders and schizophrenia (for review, see Craddock et al.\textsuperscript{85}).

In summary, molecular genetic studies point to potential risk loci of psychotic depression derived from findings in schizoaffective disorder (1q42, 22q11, 19p13), depression, bipolar disorder and schizophrenia (6p, 8p22, 10p13-12, 10p14, 13q13-14, 13q32, 18p, 22q11-13) and—though partly based on small sample sizes or on mixed samples of patients with major depression and bipolar disorder—several vulnerability genes potentially contributing to an increased risk of psychotic features in depression (eg, BDNF, DBH, DTNBP1, DRD2, DRD4, GSK-3beta, MAO-A). Although the presently available association findings ought not to be considered robust, they still seem to point to a particular role of genes either directly (DBH, DRD2, DRD4) or indirectly (DTNBP1,\textsuperscript{44} GSK-3beta)\textsuperscript{86} involved in dopamine- and glutamate-related neurotransmitter pathways for psychotic depression as opposed to serotonin receptor genes like HTR1A, HTR1B, and HTR5A suggested to constitute a major link in several networks/pathways in major depression.\textsuperscript{87}

Pharmacogenetics

It has repeatedly been shown that the treatment of psychotic depression is particularly challenging and differs from the one of nonpsychotic depression,\textsuperscript{88} which may in part be conferred by genetic factors. Applying a pharmacogenetic approach, Smeralda et al. reported association of the less active serotonin transporter 5-HTT LPR S allele with worse response to antidepressant treatment with fluvoxamine in a sample of in-patients with psychotic major depression.\textsuperscript{89} Dysbindin (DTNBP1) variation, previously suggested to be associated particularly with the subtype of psychotic depression,\textsuperscript{90} was also found to be associated with antidepressant treatment response in severely depressed patients.\textsuperscript{90} This finding was corroborated in a Spanish sample of patients with major depression, where a significant effect of the DTNBP1 rs760761 polymorphism on antidepressant treatment response was detected when taking psychotic symptoms into account.\textsuperscript{91} Recently, a possible role of the tryptophan hydroxylase 1 (TPH1) rs1800532 polymorphism has been suggested in antidepressant response in psychotic unipolar major depression.\textsuperscript{92} Several other pharmacogenetic studies in depression explicitly controlling for an influence of psychotic features failed to discern an effect of, eg, tryptophan hydroxylase (TPH) and serotonin transporter (5-HTT) gene variation on antidepressant treatment response specific to psychotic depression (eg, Serretti et al.\textsuperscript{93} and Zanardi et al.\textsuperscript{94}). One of the largest samples studied pharmacogenetically in depression so far, the STAR*D sample (ClinicalTrials.gov Identifier: NCT00021528), is noninformative regarding psychotic depression as STAR*D explicitly focused on nonpsychotic major depressive disorder.

Discussion and Future Directions

Despite some promising first results, the presently available linkage studies, association studies, and pharmacogenetic studies on psychotic symptoms in depression are difficult to interpret given the heterogeneity of samples and methods. Thus, for future studies it is suggested that stricter methodologic guidelines are considered as, eg, proposed for pharmacogenetic studies in depression in general.\textsuperscript{95} For instance, the clinical phenotype of “psychotic depression” has to be conceptualized in a more standardized way, as to date only few molecular genetic studies have actually investigated the phenotype of “psychotic depression,” while eg, suggestive risk loci for psychotic depression have only been derived from linkage findings overlapping between schizoaffective disorder, schizophrenia, and affective disorders. Thus, future studies will need to explicitly focus on a “psychotic depression” phenotype clearly distinguishing between unipolar and bipolar psychotic depression as well as between mood-congruent and mood-incongruent psychotic symptoms. Additionally, the application of dimensional instruments as for instance the OPCRIT, the Delusional Assessment Scale (DAS) or the Hopkins Symptom Checklists\textsuperscript{45,96,97} might facilitate the identification of genetic risk factors of psychotic depression by generating a more sharply defined phenotype and allow for a better comparability across studies. Comorbidity with axis I/II disorders, family history for mental disorders, severity of baseline symptomatology, number of episodes, age, sex, and ethnicity are further issues to be considered in future studies. Pharmacogenetic studies will profit from a standardized treatment design (antidepressant monotherapy) as opposed to a naturalistic treatment design prone to confounding influences of various antidepressants and neuroleptic or anxiolytic comedication, a standardized assessment of compliance (eg, therapeutic drug monitoring), homogeneous response criteria, and a sufficient duration of assessment.\textsuperscript{95}

Furthermore, as most presently available association studies in psychotic depression—particularly those investigating serotonergic genes—are based on relatively small sample sizes, in the future potential candidate genes need to be revisited in large-scale association studies. Also, genome-wide association studies (GWAS), interrogating the entire genome for association applying a hypothesis-free approach, are warranted to aid in the more robust identification of risk variants and at the same time in
discerning novel vulnerability genes of psychotic depression. Novel promising candidate genes in psychotic depression might furthermore be derived from a recent network and pathway analysis in major depression demonstrating that several depression genes showed similar topological characteristics to schizophrenia. 

Because a twin study has shown that genetic liability for depression may potentiate the influence of childhood traumata on psychotic-like symptoms, gene-environment interaction studies might contribute to a more comprehensive understanding of the complex-genetic mechanisms of psychotic depression. Furthermore, the investigation of epigenetic mechanisms such as chromosomal rearrangements, DNA cytosine methylation and hydroxymethylation or histone modifications in conjunction with transcriptome profiling and whole-genome sequencing will aid in disentangling the genetic/epigenetic underpinnings of the affective-psychotic spectrum.

The influence of genetic factors on complex traits or diseases such as psychotic depression can be further specified by investigation of so-called intermediate phenotypes, which, due to a more narrow definition, have been proposed to be closer to the underlying genetic risk factors. Promising intermediate phenotypes of psychotic depression might comprise neuropsychological, neuroendocrinological or neural activation correlates of relevant cognitive or emotional processes: eg, a significantly reduced amygdala volume has been shown to be characteristic of depressed patients with psychosis relative to depressed patients without psychosis and healthy comparison subjects and might therefore serve as an intermediate phenotype of psychotic depression in future studies. Additionally, given converging evidence for a particular role of dysbindin gene variation across affective and psychotic disorders, future studies could focus on investigating the impact of DTNBP1 variation on neuropsychological profiles such as cognitive function or prefrontal brain function as relevant in psychotic depression. Furthermore, reflexive saccades, which have been reported to be hypometric in psychotic unipolar depression, or deficits in gain of smooth pursuit eye movements demonstrated in both schizophrenia and affective disorder patients as well as their health relatives, seem to constitute valid intermediate phenotypes of psychotic depression still warranting in depth analysis including molecular genetic methodology. Rodent models of affective disorders could be helpful in the search for apt intermediate phenotypes with regard to the genetic mechanisms of psychotic depression, eg, high stress reactivity mice as a model of both schizophrenia and major depression have been shown to display cognitive deficits associated with psychotic-like behavior linked to perseveration in a reversal learning task and disrupted latent inhibition accompanied by altered dopamine 1 and 2 receptor levels in the ventral tegmental area, the cingulate cortex, and the nucleus accumbens.

With regard to the genetic underpinnings of treatment response in psychotic depression, aside from the classical pharmacogenetic approach, studies on the genetic modification of psychotic symptoms in depression by electroconvulsive therapy (ECT) might be useful, as ECT has been suggested to be particularly beneficial in delusional depression and as several studies have already reported a genetic impact on ECT response in unipolar major depression irrespective of psychotic symptoms.

Summary and Conclusion

In summary, clinical genetic studies suggest a familial aggregation and a considerable heritability (39%) of psychotic depression partly shared with schizoaffective disorder, schizophrenia, and affective disorders. Linkage studies point to potential risk loci of psychotic depression derived from risk loci in schizoaffective disorder (1q42, 22q11, 19p13) or risk loci overlapping in depression, bipolar disorder, and schizophrenia (6p, 8p22, 10p13-12, 10p14, 13q13-14, 13q32, 18p, 22q11-13). Several vulnerability genes possibly contributing to an increased risk of psychotic symptoms in depression (eg, BDNF, DBH, DTNBP1, DRD2, DRD4, GSK-3beta, MAO-A) have been implicated by association studies, again overlapping with findings in both affective disorders and schizophrenia. Pharmacogenetic studies suggest S-HTT, TPH1, and DTNBP1 gene variation in the mediation of antidepressant treatment response in psychotic depression.

The clinical and molecular genetic as well as pharmacogenetic findings in psychotic depression as outlined above are about to contribute to a better understanding of the neurobiological pathomechanism of the clinical phenotype of psychotic depression on the spectrum between affective and psychotic disorders and—given robust replication in large, independent samples—are thereby of potential (1) nosological and (2) therapeutic relevance.

(1) Back from bench to bedside, genetic studies might inspire a re-evaluation and refinement of DSM-IV categorized nosological concepts of affective and psychotic disorders, challenging the classical Kraepelinian dichotomous view and suggesting a classification of cases with both psychotic and affective symptoms as clinically seen in psychotic depression and therefore a continuum of liability to schizophrenia and affective disorders rather than a binary classification with clear-cut boundaries between these two nosological entities. Additionally, the current and still emerging body of knowledge in the field of genetic research in affective and psychotic disorders might have even more far-reaching consequences in the future by challenging the DSM concept in itself in favor of a more neurobiologically-oriented taxonomy of mental disorders. As suggested by Smoller et al. for anxiety disorders, genetic and imaging research revealing etiological mechanisms of mental disorders might infer...
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