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Research report

Commingling analysis of age-of-onset in bipolar I disorder and the morbid risk for major psychoses in first degree relatives of bipolar I probands

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ABSTRACT

Background: Age-of-onset (AO) is increasingly used in molecular genetics of bipolar I disorder (BP-I) as a phenotypic specifier with the goal of reducing genetic heterogeneity. However, questions regarding the cut-off age for defining early onset (EO), as well as the number of onset groups characterizing BP-I have emerged over the last decade with no definite conclusion. The aims of this paper are: 1) to see whether a mixture of three distributions better describes the AO of BP-I than a mixture of two distributions in different independent samples; 2) to compare the morbid risk (MR) for BP-I and for major affective disorders and schizophrenia in first degree relatives of BP-I probands by proband onset group derived from commingling analysis, since the MR to relatives is a trait with strong genetic background.
Methods: We applied commingling (admixture) analysis to the AO of three BP-I samples from Romania ($n=621$), Germany ($n=882$), and Poland ($n=354$). Subsequently, the morbid risk (MR) for BP-I and for major psychoses (BP-I, BP-II, Mdd-UP, schizoaffective disorders, schizophrenia) was estimated in first degree relatives by proband AO-group derived from admixture analysis in the Romanian sample.
Results: In the three independent samples and in the combined sample two- and three-AO-group distributions fitted the empirical data equally well. The upper EO limit varied between 21 and 25 years from sample to sample. The MR for both BP-I and for all major psychoses was similar in first degree relatives of EO probands ($AO \leq 21$) and in relatives of intermediate-onset probands ($AO=22–34$). Significant MR differences appeared only when comparing the EO group to the late-onset (LO) group ($AO > 34$). Similar to Mdd-UP and schizophrenia, a significant MR decrease in proband first degree relatives was visible after proband AO of 34 years. Under the three-AO-group classification the MR for both BP-I and all major psychoses in first degree relatives did not differ by relative sex in any proband AO-group. Under the two-AO-group classification female relatives of LO probands ($AO > 24$) had a significantly higher MR for all major psychoses than male relatives, while there was no sex difference for the relatives of EO probands.
Limitations: MR was not computed in the German and Polish samples because family data were not available and 34% of the relatives of the Romanian probands were not available for direct interview.
Conclusion: Similar to other clinical traits, the MR for major psychoses to relatives failed to support a three-AO-group classification in BP-I suggesting that this is not more useful for the molecular analysis than a two-AO-group classification.

1. Introduction

Age-of-onset (AO) is considered a phenotypic specifier that might reduce the genetic heterogeneity of the disorders, being

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increasingly used in the molecular genetics of bipolar I disorders (BP-I).

In this context, a debate about the cut-off point for defining the early onset (EO) versus the late onset (LO) in BP-I disorder, as well as about the number of onset groups characterizing this disorder, has emerged over the last decade, especially after the publication of two papers by Bellivier et al. (2001, 2003) that applied admixture analysis to the AO of two small BP samples finding a mixture of three normal distributions as the best fit to the observed data. Some of the subsequent studies (Lin et al., 2006; Manchia et al., 2008, Hamshere et al., 2009; Tozzi et al., 2011, Ortiz et al., 2011) have replicated the three AO-group model as a best fit for the AO distribution in BP-I disorder, although with variable upper limits for the early onset (18–22 years). However, when attempting to find clinical differences among the AO groups derived by admixture analysis, with few exceptions, the majority of studies restricted the comparison to two groups – the EO and the LO groups – the intermediate onset group being usually ignored.

The proportion of cases included in the three onset groups determined through admixture analysis varies widely from study to study and even within the EO group defined as AO < 21 years the variation ranges from 21% (Bellivier et al., 2001) to 79% (Lin et al., 2006) in different samples.

But not all studies applying admixture analysis found the best fit of BP-I onset under a three-group model. Kennedy et al. (2005) found the best fit for a *two-AO-group model* with age 40 *as cut-off* for EO with a peak incidence for mania in the age band 21–25 years. Javaid et al. (2011) found the *two onset group model* the most adequate for the AO distribution of BP-I in a Canadian sample. The cut-off between EO and LO was set at *age 22*, the intersection point between the density distribution curves.

Summarizing the formal aspects of the results provided by admixture studies so far, we may observe that the cut-off point for the early onset BP-I varies from 18 (Ortiz et al., 2011) to 40 years (Kennedy et al., 2005) and the proportion of cases included from 21 to 79%, depending on the sample. So, no universal standards could be validated for BP-I disorder. We note that the differences in the number of identified onset groups and age limits of these groups in the cited studies are not due to differences in AO definition. All studies used the retrospective measurement based on patient interview and clinical records considering the age at which the patients first met either DSM-IV criteria for BP-I disorder (the majority of the studies) or DSM-III-R criteria (Lin et al., 2006) as the illness AO. The DSM-IV criteria do not differ significantly from DSM-III-R criteria for BP-I disorder.

1.1. Clinical differences in onset groups derived by admixture analysis

1.1.1. Clinical differences in three-AO-group classifications in BP-I

Bellivier et al. (2001) compared certain clinical features of BP-I among the three onset groups found in their sample. They found no significant difference between the EO and the intermediate onset groups in terms of psychosis during affective episodes, family history of affective disorders, or number of suicide attempts. Differences emerged only in the comparison of EO versus LO group.

Lin et al. (2006) compared the three onset groups to one another in a sample of 211 BP-I patients and found no clinical difference between the intermediate group (AO=22–28) and the LO group (AO > 28) with respect to psychosis, rapid cycling, comorbidity with panic and obsessive compulsive disorders, drug and alcohol abuse, suicide attempts, or episode frequency. These clinical features were significant only in the comparison of the EO group (79.7% cases) with the LO group (13.1% cases).

Hamshere et al. (2009) also contrasted all three AO groups revealed by admixture analysis. They found significant differences for clinical variables (positive family history for affective disorders, rapid-cycling, suicide attempts) only for comparisons between the EO (AO ≤ 22 years) and the LO group (AO ≥ 40 years) but not for comparisons between the intermediate onset (AO=25–37 years) and the LO group.

In the study by Ortiz et al. (2011), the intermediate AO group was not considered for clinical comparison. The EO group (AO < 19) was associated with a stronger family history of affective disorders, psychotic symptoms in the manic episode, suicidal behavior, co-morbid anxiety disorders**,** and more females compared to the LO group (AO > 32). The AO in females was significantly younger than in males in the total sample ($p < 0.01$).

Tozzi et al. (2011) found that the three-AO-group model was marginally better than the two-AO-group model and graphically the intermediate group was completely overlapped by the other two groups. So, they subdivided the sample ($n=954$) into two groups for the analysis of clinical differences choosing the age 25 as cut-off for the EO because the probability of belonging both to the EO and the LO group was equal at this age. They failed to find differences regarding family history of affective disorders, psychosis, and illness severity between the EO and LO group. Only the suicide attempts were more frequent in the EO group. In this sample the AO was younger in females than in males ($p=0.02$).

Coryell et al. (2013) applied mean AO thresholds resulting from previous admixture studies to subdivide their sample into three AO groups (≤ 20, 21–29, ≥ 30 years). There were no differences in terms of psychotic features, frequency of manic/hypomanic episodes, functional impairment, or lifetime comorbidity among the AO groups. Only the drug abuse and panic attacks were more frequent in the EO group when compared with the LO group.

In summary, all studies that investigated clinical characteristics of BP-I according to a three-AO-group model derived from admixture analysis failed to evidence significant differences either between the intermediate onset group and the LO group or between the EO and the intermediate onset group.

1.1.2. Clinical differences in two-AO-group classifications in BP-I

Kennedy et al. (2005) reported clinical differences between early onset (AO < 40 years) and late onset (AO > 40 years) with regard to family history of affective disorders ($p < 0.01$**)** and psychosis ($p < 0.05$). Females had a younger onset than males ($p < 0.01$).

Javaid et al. (2011) found no significant difference between the EO and the LO group with respect to the presence of psychosis and axis I comorbidity when comparing the EO and the LO groups defined by the cut-off age of 22 years.

No admixture study has addressed the issue of the morbid risk (MR) for major affective disorders or for all major psychoses to first degree relatives of probands to differentiate among onset groups generated by admixture analysis.

In this context, the objectives of our study are as follows: 1) to see whether a mixture of three distributions better describes the AO of BP-I than a mixture of two distributions in different independent samples, recruited under similar conditions (consecutive hospital admissions); 2) to compare the MR for BP-I and for major affective disorders and schizophrenia in first degree relatives of BP-I probands by proband onset group derived from commingling analysis, since the MR to relatives is a trait with strong genetic background. We consider the MR both for BP-I and for all major psychoses together (BP-I, BP-II, recurrent unipolar major depression, schizoaffective disorders, schizophrenia) since genome-wide association meta-analyses have shown an overlapping molecular basis for all these disorders **(**Craddock et al., 2009;