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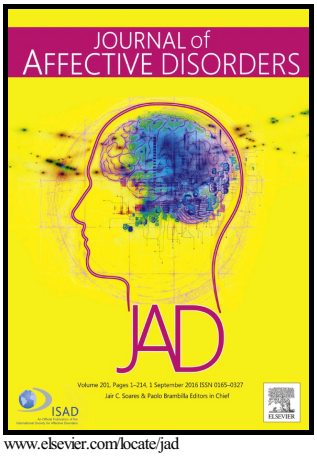

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Association between genetic variation in the myo-inositol monophosphatase 2 (*IMPA2*) gene and age at onset of bipolar disorder

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Keywords: early-onset, IMPA2, genetics, bipolar disorder.

Abstract

Introduction

The age at onset of bipolar disorder (BD) has significant implications for severity, duration of affective episodes, response to treatment, and psychiatric comorbidities. It

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has been suggested that early-onset BD (EO-BD) could represent a clinically distinct subtype with probable genetic risk factors different from those of late-onset BD (LO-BD). To date, several genes have been associated with BD risk but few studies have investigated the genetic differences between EO-BD and LO-BD. The aim of this study was to evaluate if variants of the gene coding for myo-inositol monophosphatase (*IMPA2*) are linked to age at onset of BD.

Method

235 bipolar patients were recruited and assessed. The final sample consisting of 192 euthymic individuals, was compared according to the age at onset. Polymorphisms were genotyped in the *IMPA2* gene (rs669838, rs1020294, rs1250171, and rs630110). Early-onset was defined by the appearance of a first affective episode before the age of 18.

Results

The analyses showed that in the genotype distribution rs1020294 (p= 0.01) and rs1250171 (p= 0.01) were associated with the age at onset. The significant effect remained only in the rs1020294 SNP in which G carriers were more likely to debut later compared to patients presenting the AA genotype (p= 0.002; OR= 9.57, CI95%[2.37-38.64]). The results also showed that EO-BD tended to experience more alcohol misuse (p= 0.003; OR= 0.197, CI95%[0.07-0.58]) compared to LO-BD.

Conclusions

Our results provide evidence for genetic differences between EO-BD and LO-BD at the *IMPA2* gene as well as clinical differences between subgroups with therapeutic implications.

1. Introduction

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Bipolar disorder (BD) is a severe recurrent illness characterized by severe mood symptoms, including episodes of mania or hypomania and depression, occurring mainly with a typical cyclical course (Barnett & Smoller, 2009). Moreover it is a leading cause of disability worldwide which affects more than 1% of the world's population (Grande et al., 2016). Despite the impact that BD has in our society, little is known about its etiopathogenesis apart from a multifactorial background with an estimated heritability between 60-80% (Mühleisen et al., 2014).

BD is both genetically and phenotypically heterogeneous and may present a wide range of symptoms. Due to this heterogeneity, diagnosis of BD is complex and the disorder is commonly misdiagnosed especially during the initial stages of the illness as major depressive disorder (Smith et al., 2011), schizophrenia (Akiskal, 1999) or borderline personality disorder (Akiskal et al., 2000; Levitt et al., 1990; Ruggero et al., 2009). Regarding adolescents with BD, they are often misdiagnosed with attention deficit hyperactivity disorder (ADHD) or depression (Citrome et al., 2005). A late diagnosis implies a delay with treatment and consequently a poorer clinical outcome (Elanjithara et al., 2011). Previous studies have shown that the longer BD is left untreated, the more severe the clinical outcomes, such as increased rates of suicidal behavior, a higher number of mood episodes, and increased social difficulties (Drancourt et al., 2013; McCraw et al., 2014). Thus, early detection followed by early intervention and adequate treatment is critical to improve the prognosis and course of the disorder (Vieta et al. 2018).

Disentangling the phenotypic heterogeneity of BD before performing genetic analysis has been suggested as a relevant strategy for identifying BD susceptibility genes (Szczepankiewicz, 2013). It has been postulated that clinical sub-phenotypes of BD may identify more etiologically homogenous subset of patients, which can be

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studied with increased power to detect genetic variation (Belmonte et al., 2011). Studies have considered age at onset a phenotypic specifier (Grigoroiu-Serbanescu et al., 2014) and have identified early-onset BD (EO-BD) subgroup as a clinically distinct BD subtype with specific clinical features and outcomes and conceivably distinct genetic risk factors (Bellivier et al., 2003; Geoffroy et al., 2013; Lin et al., 2006; Manchia et al., 2008; Tozzi et al., 2011). Previous studies have identified associations between EO-BD patients and high incidence of psychosis (Javaid et al., 2011), greater rates of comorbid anxiety disorder and substance abuse (Cate Carter et al., 2003; Perlis et al., 2004), rapid cycling (Cate-Carter et al., 2003; Lin et al., 2006; Post et al., 2010), poorer lithium-response (Leboyer et al., 2005), more suicide attempts (Cate-Carter et al., 2003; Geoffroy et al., 2013; Lin et al., 2006; Perlis et al., 2004) and worse prognosis compared to late-onset BD (LO-BD) patients. EO-BD has also been correlated with impaired cognitive and social functioning as well as with reduced quality of life (Dell'Osso et al., 2016). In addition, EO-BD patients have been shown to be genetically more homogenous than LO-BD patients (Leboyer et al., 2005) showing a higher familial loading (Etain et al., 2010; Geoffroy et al., 2013; Grigoroiu-Serbanescu et al., 2001; Mick & Faraone, 2009; Ortiz et al., 2011; Schurhoff et al., 2000).

From a genetic approach, the possible differences between EO-BD and LO-BD patients remain inconclusive, since some studies have reported genetic heterogeneity between early and late onset involving different genetic variants (Mathieu et al.,2010; Dizier et al., 2012; Grigoroiu-Serbanescu et al., 2015) and others have failed to find significant results (Belmonte et al, 2011). Candidate gene association studies have suggested that polymorphisms of myo-inositol monophosphatase 2 gene (*IMPA2*) confer risk to BD (Bloch et al., 2010; Ohnishi et al., 2007; Sjoholt et al., 2004). *IMPA2* is a protein-coding gene for a catalytic protein that converts inositol monophosphate into

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free inositol through dephosphorylation (Bloch et al., 2010). Inositol is an important intracellular signalling molecule involved in the expression regulation of more than 712 genes (Jesch et al., 2005). Previous studies have suggested that an overactive inositol phosphatase signal transduction pathway may underlie mania (Hardwood, 2005). Furthermore, response to lithium, a common pharmacological treatment for BD, has been thought to have a genetic basis (Hou et al., 2016) with evidence suggesting that lithium plays an important role in the phosphoinositide pathway by inhibiting myo-inositol monophosphatase activity resulting in lower inositol levels (Vandal & Parthasarathy, 1995).

The aim of this study was to investigate genetic variability in the *IMPA2* gene according to age at onset of BD as well as to discriminate clinical and socio-demographic differences between EO-BD and LO-BD patients. We aim to define the possible role that variations of *IMPA2* gene may have on the onset of BD. These results may shed some light when it comes to discerning particularities of subgroup of patients diagnosed with BD and foresight their prognosis.

2. Materials and Methods

2.1 Subjects

Two-hundred and thirty-five Caucasian bipolar I or II outpatients were consecutively recruited and assessed to participate in this study. After ruling out all patients that did not fulfil euthymia criteria at inclusion and during assessment period (defined as a score ≤ 8 on the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960; Ramos-Brieva & Cordero, 1986) and a score ≤ 6 on the Young Mania Rating Scale (YMRS) (Colom et al., 2002; Young et al., 1978)), the final sample consist of 192 individuals. All patients were recruited from the Bipolar Disorder Program (BDP) at the

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Hospital Clinic of Barcelona and from mental health services in Oviedo. The BDP has been conducting a prospective data collection on course of illness of all patients in the program since 1992. This systematic follow up bimonthly systematically collects clinical and socio-demographic data of all patients included in the BDP. Patients are subsequently followed up and monitored. All patients included in the database provided written informed consent for the collection of their data to be used for research purposes and their identity remains confidential. This cross sectional analysis includes both prospective and retrospective data, meaning that the former was obtained from the follow up carried out at the BDP and the latter from the patients at baseline assessment.

Inclusion criteria were as follows: (a) DSM-IV criteria for bipolar I or bipolar II disorder, (b) age of 18 years or older, (c) descended from at least two generations of Caucasian, (d) meet criteria for euthymia and (e) written informed consent. Exclusion criteria included mental retardation (defined as IQ < 70) and/or severe organic disease. Approval from each institution's ethics committee was obtained.

2.2 Assessment

Different sociodemographic and clinical variables were collected, such as age, gender, education, marital status, employment, psychiatric diagnoses, age of first episode, number of hospitalizations, number and polarity of previous episodes, history of psychotic symptoms, psychotic symptoms during first episode, psychotic depression, delusions, hallucinations, melancholy, atypical symptoms, rapid cycling, history of suicidal behavior and ideation including methods, psychiatric family background, alcohol misuse, response to lithium and current treatment. All of them were gathered by means of a semi-structured interview based on the Structured Clinical Interview of DSM

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Disorders (SCID). Relevant data from medical records were also considered. The HDRS was used to assess depressive features, while the YMRS was used to assess manic features.

In order to evaluate functional outcome of subjects with BD, the Functioning Assessment Short Test (FAST) assessment was administered. This scale is a valid and reliable instrument; it was developed with the aim to identify the main difficulties experienced by the mentally ill including those with BD (Rosa et al., 2007). This assessment scale is composed of 24 items that evaluate the following six specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. Items are rated on a 4-point scale where 0 = no difficulty, 1 = mild difficulty, 2 = moderate difficulty, and 3 = severe difficulty. The global score is obtained when the scores of each item are summed. FAST scores can range from 0 to 72. Higher scores are indicative of poor functioning (Rosa et al., 2007).

Trait-impulsivity was assessed by means of the Barratt Impulsiveness Scale (BIS-11) based on principal component analysis of the scale by Patton et al. (1995). It is a self-administered questionnaire consisting of 30 questions. Answers are quoted on a four point Likert scale (1 = rarely/never to 4 = almost always/always). Overall scores range from 30-120 with higher scores indicating greater impulsivity. Non-psychiatric controls generally score between 50-60 (Swann et al., 2002). BIS-11 is comprised of three main subscales. The attentional-cognitive subscale measures tolerance to cognitive complexity and persistence. The motor subscale measures the tendency to act impetuously and the non-planning impulsivity subscale evaluates the absence of weighing up future consequences of action.

The Temperament Scale of Memphis, Pisa, Paris, and San Diego- Auto questionnaire (TEMPS-A), 110 questions version, was utilized to measure five

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temperament domains: depressive (items 1-21), cyclothymic (items 22-42), hyperthymic (items 43-63), irritable (items 64-84), and anxious (items 85-110) (Akiskal et al., 2005; Dembinska-Krajewska & Rybakowski, 2014).

The age at onset was defined by the age at which the first mood episode occurred. The first mod episode was defined by the presence of a manic, hypomanic or major depressive episode as diagnosed by a Structured Clinical Interview for Axis I DSM-IV Disorders (SCID). The threshold and cut off of age at onset before 18 years for early-onset was determined on the basis of previous studies (Carter et al., 2003; Perlis et al., 2004; Schurhoff et al., 2000). Level of education was defined by highest education completed and categorized into three levels: completion of primary education, completion of secondary education, and completion of a degree program at University. Lithium response was categorized into two categories: non-responders (NR) versus partial responders (PR) or excellent responders (ER). The level of response to lithium was assessed based on the following criteria: NR: all patients included in this category were those who have presented a reduction of less than 50% of episodes after lithium prescription, no change or worsening; patients who required electroconvulsive therapy also fell into this category. PR: this group consisted of patients who presented a reduction of 50% of episodes after the introduction of lithium or those who despite fulfilling excellent responder criteria were on polytherapy (other mood stabilizer, antidepressant, or antipsychotics) at the time of their inclusion to the study. ER: included patients who did not present an affective episode since the start of lithium intake or those who have presented a substantial reduction in excess of 50% of relapses; all patients included in this group were on monotherapy. Suicide attempt was defined as self-injury act committed with some intention to die. Violent suicide attempts included methods such

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as hanging, deep cutting, defenestration, and electrocution. Other methods such as overdoses and self-poisoning were considered non-violent.

2.3 DNA Preparation and Genotyping

DNA was extracted from blood samples according to standard protocols. Single nucleotide polymorphisms (SNPs) at *IMPA2* gene (rs669838, rs1020294, rs1250171, and rs630110) were selected based on literature and the SYSNPS program (www.sysnps.org). SNPs were selected with SYSNPS program only if they were tag SNPs of the candidate gene with Minor Allele Frequency (MAF) >0.3. This MAF criterion was used to increase the statistical power. Genotyping, blind to clinical assessment, was performed by competitive quantitative PCR using allele specific probes with FRET signal detection. A random subsample of individuals was re-genotyped in order to confirm the pattern reproducibility.

The percentage of genotyping success for each SNP according to the total sample (n=197) was: 98% for rs669838 (n=193), 99% for rs1020294 (n=195), 98.5% for rs1250171 (n=194), and 98.5% for rs630110 (n=194).

2.4 Statistical Analyses

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 23). Descriptive statistics was used to determine the means and frequencies of variables. Pearson´s chi-square contingency analysis and independent samples t-test were used to test group differences between EO-BD and LO-BD groups in socio-demographic variables, clinical variables, and psychological dimensions. Hardy-Weinberg Equilibrium (HWE) for genotypic and allelic distribution

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frequencies was calculated using chi-squared test. The genotypic and allelic frequencies were compared between EO-BD and LO-BD using chi-squared analysis. Fisher´s exact values were computed wherever necessary. Odds Ratio (OR) and confidence interval 95% (CI95%) were calculated to assess the relative risk conferred by a specific allele or genotype. A binary logistic regression model was used to identify factors associated with LO-BD, with age at onset (EO-BD vs. LO-BD) as the dependent variable; the variables introduced in the model were mainly based on statistical significance in univariate analysis (alcohol misuse, atypical symptoms, T- carriers of *IMPA2*- rs1250171, and G-carriers of *IMPA2*-rs102094). However, other variables previously described in literature were also considered (rapid cycling, suicide attempts, and psychotic symptoms). Statistical significance level was set at $p<0.05$ for all statistical tests.

3. Results

3.1 Descriptive Statistics

Socio-demographics and clinical characteristics of the whole sample are shown in Table 1. The sample comprised of a total of 197 euthymic BD subjects with mean age of 47.32 ±12.58 and 51.2% males. Genotype distributions of all SNPs were found to be in HWE (p= 0.49 for the *IMPA2*-rs669838; p= 0.6 for the *IMPA2*-rs1020294; p= 0.97 for the *IMPA2*-rs1250171; p= 0.97 for the *IMPA2*-rs630110). Atypical symptoms were significantly more frequent in EO-BD patients than in LO-BD (X^2 = 4.223, p= 0.04), EO-BD patients were more likely to present alcohol misuse (X^2 = 11.568, p= 0.001).

LO-BD patients were found to score significantly higher on the HDRS (t= -2.21, p= 0.03) and TEMPS depressive subtest (t= -3.03, p= 0.004). LO-BD also scored significantly higher on the FAST autonomy subdomain (t= -2.15, p= 0.04). On the

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contrary, EO-BD exhibited higher scores on the non-planning impulsivity BIS-II subscale (t= 2.03, p= 0.04). No significant differences between both groups were found concerning the remaining variables (see Table 1).

3.2 Single Marker Analysis

Single marker analysis revealed in the genotype distribution that variants *IMPA2*-rs1020294 (X^2= 10.844; p= 0.01) and *IMPA2*-rs1250171 (X^2= 9.894; p= 0.01) were associated with the age at onset of BD (Table 2). Regarding the allele distribution, carriers of the G alelle of the *IMPA2*-rs1020294 gene were more likely to have LO-BD compared to AA genotype (X^2= 7.96; p= 0.01) (Table 3) whereas the significant results for *IMPA2*-rs1250171 were not shown in the allele distribution. There were no significant associations at the genotypic and allelic level for the variants rs669838 and rs630110.

3.3 Multivariate Analysis

Variables that were found to be statistically significant in the univariate analyses (alcohol misuse, atypical symptoms, G carriers of *IMPA2*-rs102094, T carriers of *IMPA2*-rs1250171) along with variables found to be associated with BD age at onset in previous studies (rapid cycling, suicide attempt, psychotic symptoms) were included in the multivariate analysis. The only variables that survived the binary logistic regression were G-allele carriers of *IMPA2*-rs102094 (B= 2.258, X2= 10.051, p= 0.002, OR= 9.565, CI95% [2.368-38.638]) and alcohol misuse (B= -1.625, X2=8.613, p=0.003, OR=0.197, CI95% [0.066-0.583]) (Table 4).

4. Discussion

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Our results suggest that age at onset of bipolar disorder seems to be associated with genetic variability at *IMPA2* polymorphism rs1020294. Despite that in the genotype distribution rs1020294 and rs1250171 resulted significantly associated with the age at onset of BD, when considering the allele distribution, the significant effect was only shown in the rs1020294 SNP in which G carriers were more likely to debut BD later compared to carriers of the AA genotype. This association survived in the multivariable analysis. Therefore, our findings suggest that the G-allele at *IMPA2*-rs1020294 may play a protective role and may be facilitating delay in the illness onset. Moreover, EO-BD patients were more likely to present increased likelihoods of misusing alcohol and presence of atypical symptoms compared to LO-BD patients.

The potential important role of the phosphoinositide pathway in the onset of BD has already been pointed out. Similarly, a recent genome wide association study (GWAS), which compared EO-BD patients with healthy controls, revealed that genetic variants in different genes involved in phosphoinositide signaling pathway (*PLEKHA5* and *PLCXD3*) might confer vulnerability to EO-BD (Jamain et al., 2014). These findings and alongside with ours are indicative that variations in the phosphoinositide pathway may be influencing age at onset in bipolar disorder. The relevance of this biological pathway relays on the fact that myo-inositol monophosphatase dephosphorylates inositol monophosphate, regenerating free inositol. Lithium, considered as the gold-standard treatment for bipolar disorder, has been shown to inhibit IMPA2 activity and decrease levels of inositol. It is hypothesized that lithium exerts its therapeutic effect partially through inositol regulation. Therefore, dysfunction of inositol caused by IMPA2 irregularity may contribute in part to the pathophysiology of bipolar disorder (Bloch et al., 2010).

Our results suggest that the presence of G alelle of the *IMPA2*-rs102094 gene may reduce the vulnerability of an early-onset. Interestingly, genetic variability of *IMPA2* has

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been previously associated with poor response to lithium (Dimitrova et al., 2004, Mitjans et al., 2015) and increased suicidal behavior in BD patients (Jimenez et al., 2013). However, in our study there were no significant differences between EO-BD and LO-BD groups in terms of response to lithium, thoughts of suicide, or suicidal behavior. All in all, our results comport with previous literature indicating a significant potential role of genetic variability of phosphoinositide signaling pathway in the emergenece and prognosis of bipolar patients, and more specifically reinforcing the idea that IMPA2 may be a genetic susceptibility factor for this psychiatric condition (Sjoholt et al., 2004; Serretti et al., 2010).

Furthermore, our results displayed clinical differences between EO-BD and LO-BD patients. The observed association of EO-BD and higher rates of alcohol misuse comport with results obtained in previous studies (Dell'Osso et al., 2016). This relationship is not surprising since during the adolescence period it is characteristic to act more impulsively without recognizing the consequences and the propensity to seek out new and potentially dangerous situation is typical (National Institute on Alcohol Abuse and Alcoholism, 2006). In addition, as mentioned earlier, BD is often difficult to identify during the initial stages and it is often misdiagnosed due to atypical symptoms. Here our results support the previous findings and suggests that EO-BD group is indeed associated with atypical symptoms which may complicate diagnosis. It has been estimated that among patients seeking treatment after the first episode, 34% often receive other diagnoses (Evans, 2000).

Contrary to other studies (Ortiz et al., 2011; Tozzi et al., 2011; Vande-Voort et al., 2016), we did not find statistically significant differences between EO-BD and LO-BD groups in regards to rapid cycling, number of hospitalizations, and suicide attempts. Previous studies have reported higher number of manic, depressed, and hypomanic episodes experienced by EO-BD patients (Schurhoff et al., 2000) while studies focused on BD staging have suggested that older age at onset BD patients tend to experience fewer

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episodes (Grande et al., 2014). In our study, EO-BD patients experienced higher number of manic, depressed, and hypomanic episodes in general terms compared to LO-BD patients however statistical significance was not reached. This may be due to the small sample size especially of the EO-BD group.

Although the patients in our study fulfilled strict criteria for euthymia and present low levels of manic and depressive symptoms as measured with appropriate scales, our findings reveal an association between sub-threshold depressive symptoms, depressive temperament and LO-BD. Our results confirm previous findings that reveal that LO-BD patients often show depressive polarity (Forty et al., 2009; Kassem et al., 2006), depressive temperament (Azorin et al., 2013) and even increased likelihood for misdiagnosis of major depressive disorder (Zhang et al., 2016). Consistent with previous studies, our findings suggest an association between subsyndromal depressive symptoms, a worse prognosis, and possible functional and cognitive impairment (Bonnin et al., 2012). However, it is important to note that cognitive impairment among BD patients is highly heterogeneous and high cognitive reserve may predict neurocognitive performance in BD patients (Grande et al., 2017). In addition, though our results indicate that EO-BD patients scored higher on non-planning impulsivity BIS-11, there was no significant difference in the BIS-11 total score thus suggesting non-overall differences in impulsivity between EO-BD and LO-BD groups. These findings are indicative that there are clinical differences between EO-BD and LO-BD patients and may aid clinicians to provide effective and individualized treatment options.

Some limitations should be considered in this study. First of all, to date there is no standard consensus on the definition of EO-BD. Nevertheless, the thresholds of this study are in line with previous studies (Perlis et al., 2004; Schurhoff, et al., 2000). Secondly, SNPs that showed significant association to age at onset are located in an intronic region

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and its functional significance has not yet fully been described. However, these variants could be in linkage disequilibrium with functional ones or they could be affecting splice sites as has been described for other intronic variability (Baralle & Baralle, 2005; Jimenez et al., 2013). Though the small effect size of the results, they are in line with previous candidate gene association studies that indicate the majority of genetic variants in BD tend to have small effect sizes (Craddock & Sklar, 2013; Gratten et al., 2014). Large sample sizes are needed to detect an association and even with large sample sizes, the polymorphism will only weakly increase the risk of the disorder (Kennedy et al., 2015). It is important to note that although there were associations between some variables and the onset of BD, we cannot determine if these variables are causative. In addition, the sample size of our sample is relatively small thus potentially decreasing the statistical power and effect sizes. Nevertheless, results are in line with bibliography. Lastly, the retrospective nature of the interview in some aspects may have been influenced by recall bias.

Despite limitations, our data indicate that genetic variability in the *IMPA2* gene accounts for some weight related to the onset of BD and that EO-BD and LO-BD groups display clinical differences. We believe that the obtained data will provide further insight for future genetic association studies and aid the search for genetic biomarkers. These findings in the near future may offer potential biological explanations to the clinical differences observed in the BD subtypes. We hope this will aid future studies and progress to the identification of genetic biomarkers that would offer clinicians an innovative tool for screening at early stages of the illness and thus increase diagnostic accuracy and offer early treatment to potentially improve the prognosis of bipolar patients.

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Acknowledgements

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Conflict of Interest

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Contributors

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Table 1. Clinical and socio-demographic characteristics of early and late-onset bipolar disorder subjects.

	Total N = 197	**Early Onset N = 32**	**Late Onset N = 165**	**Statistics**
Qualitative	**N(%)**	**N(%)**	**N(%)**	
Sex (Male)	101 (51.2)	16 (50.0)	85 (51.5)	X^2= 0.025, p= 0.88
Marital status (Married)	113 (57.4)	17 (53.1)	96 (58.2)	X^2= 0.280, p= 0.60
Employment status (unemployed)	127 (66.1)	20 (62.5)	107 (66.9)	X^2= 0.228, p= 0.63

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(n=192; EO=32, LO=160)				
Level of education (n=191; EO=30, LO=161)				X^2= 4.580, p= 0.10
Primary or less	59 (30.9)	7 (23.3)	52 (32.3)	
Secondary	69 (36.1)	16 (53.3)	53 (32.9)	
University	63 (33.0)	7 (23.3)	56 (34.8)	
Diagnostic BD type I	149 (75.6)	25 (78.1)	124 (75.2)	X^2= 0.129, p= 0.72
Family history of psychiatric pathology (n=196; EO=31, LO=165)	123 (62.8)	18 (58.1)	105 (63.6)	X^2 = 0.347, p= 0.56
Family history of affective disorders (n=196; EO=31, LO=165)	112 (57.1)	17 (54.8)	95 (57.6)	X^2 = 0.080, p= 0.78
Family history of suicide (n=187; EO=31, LO=156)	32 (17.1)	7 (22.6)	25 (16.0)	X^2= 0.783, p= 0.38
Thoughts of suicide (n= 195;EO=32, LO=163)	137 (70.3)	24 (75.0)	113 (69.3)	X^2= 0.412, p= 0.52
Suicide attempt (n=196; EO= 32, LO=164)	68 (34.7)	13 (40.6)	55 (33.5)	X^2= 0.594, p= 0.44
Violent suicide attempt (n=63; EO=11, LO=52)	34 (54.0)	6 (54.5)	28 (53.8)	X^2 = 0.002, p= 0.97
Psychotic symptoms (n=194; EO=32; LO=162)	118 (60.8)	24 (75.0)	94 (58.0)	X^2 = 3.232, p= 0.07
Psychotic symptoms during first episode (n=190; EO=31; LO=159)	77 (40.5)	12 (38.7)	65 (40.9)	X^2 = 0.051, p= 0.82
Atypical symptoms (n=185; EO=31; LO=154)	40 (21.6)	11 (35.5)	29 (18.8)	X^2= 4.223, **p= 0.04**
Psychotic depression (n=183; EO=31; LO=152)	39 (21.3)	6 (19.4)	33 (21.7)	X^2= 0.85, p= 0.77
Delusions (n=189; EO=31, LO=158)	122 (64.6)	22 (71.0)	100 (63.3)	X^2= 0.667, p= 0.41
Hallucinations (n=188; EO=30, LO=158)	37 (19.7)	6 (20.0)	30 (19.0)	X^2= 0.004, p= 0.95
Rapid cycling (n= 189; EO=31, LO=158)	28 (14.8)	6 (19.4)	22 (13.9)	X^2= 0.606, p= 0.44
Melancholy (n= 187, EO= 31, LO=156)	48 (25.7)	10 (32.3)	38 (24.4)	X^2= 0.846, p= 0.36
Alcohol misuse (n=195; EO=32, LO=163)	105 (53.8)	26 (81.3)	79 (48.5)	X^2= 11.568, **p= 0.001**
Responders to lithium (n=141; EO=26, LO=115)	129 (91.5)	23 (88.4)	106 (92.2)	X^2= 2.471, p= 0.29
Current Medications				
Mood Stabilizers	176 (89.3)	30 (93.8)	146 (88.5)	X^2= 0.780, p= 0.34
Antipsychotics	124 (62.9)	19 (59.4)	105 (63.6)	X^2= 0.209, p= 0.65
Antidepressants	72 (36.5)	10 (31.3)	62 (37.6)	X^2= 4.62, p= 0.50
Benzodiazepines	98 (49.7)	13 (40.6)	85 (51.5)	X^2= 1.271, p= 0.26
Quantitative	**Mean (S.D)**	**Mean (S.D)**	**Mean (S.D)**	
Age	47.32(12.58)	43.78(12.49)	48.00(12.53)	t(195)= -1.74, p= 0.08
Age at onset	29.74(12.63)	15.59 (1.46)	32.48(11.99)	t(184.25)= -17.438, **<0.001**
Number of episodes				
Mania	4.04 (5.48)	6.10 (8.23)	3.66 (4.70)	t(32.83)= 1.57, p= 0.13
Hypomania	2.34 (3.14)	3.32 (4.15)	2.14 (2.86)	t(137)= 1.71, p= 0.09
Depressed	7.04 (7.64)	9.16 (9.01)	6.63 (7.29)	t(182)= 1.71, p= 0.09
Mixed	0.76 (1.80)	1.45 (2.61)	0.61 (1.55)	t(24.38)= 1.47, p= 0.16
Number of	2.78 (3.69)	2.97 (3.77)	2.78 (3.70)	t(193)= 0.26, p= 0.79

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hospitalizations				
Assessment Scales				
HDRS	3.78 (2.76)	2.78 (2.52)	3.95 (2.76)	t(192)= -2.21, **p= 0.03**
YMRS	1.18 (1.91)	0.91 (1.65)	1.19 (1.91)	t(192)= -0.77, p= 0.44
FAST				
Autonomy	3.40 (3.35)	2.50 (2.42)	3.59 (3.49)	t(59.75)= -2.15, **p= 0.04**
Occupational Functioning	8.81 (6.10)	7.78 (6.32)	9.11 (6.03)	t(192)= -1.13, p= 0.26
Cognitive Functioning	6.11 (3.77)	5.84 (3.55)	6.17 (3.84)	t(192)= -0.45, p= 0.66
Finances	1.37 (1.74)	1.69 (1.87)	1.30 (1.70)	t(192)= 1.15, p= 0.25
Interpersonal relationships	4.53 (3.45)	3.53 (3.39)	4.77 (3.43)	t(192)= -1.86, p= 0.06
Leisure time	2.26 (1.93)	1.88 (1.70)	2.34 (1.98)	t(192)= -1.24, p= 0.22
Total	26.37(14.31)	23.22(13.41)	27.15(14.44)	t(192)= -1.42, p= 0.16
BIS-11				
Non-planning impulsivity	24.48 (5.12)	26.16 (4.24)	24.17 (5.21)	t(193)= 2.03, **p= 0.04**
Motor	21.77 (5.75)	21.75 (5.71)	21.74 (5.80)	t(193)= 0.01, p= 1.00
Cognitive-attentional	18.77 (3.94)	17.97 (3.77)	18.88 (3.98)	t(193)= -1.20, p= 0.23
Total	65.02(11.78)	65.79(10.95)	64.74(12.10)	t (193 = 0.47, p= 0.64
TEMPS-A				
Depressive	10.23 (4.05)	8.69 (2.82)	10.5 (4.20)	t(61.79)= -3.03, **p= 0.004**
Cyclothymic	8.60 (5.47)	7.22 (5.49)	8.79 (5.43)	t(192)= -1.49, p= 0.14
Hyperthymic	8.95 (4.60)	8.13 (4.72)	9.06 (4.58)	t(192)= -1.05, p= 0.29
Irritable	4.71 (3.96)	3.59 (3.07)	4.86 (4.05)	t(192)= -1.67, p= 0.10
Anxious	10.14 (5.98)	8.25 (4.98)	10.46(6.11)	t(192)= -1.92, p= 0.06

Bold text in the table indicates significant values
EO-BD = early onset bipolar disorder patients; LO-BD = late onset bipolar disorder patients;HDRS= Hamilton Depression Rating Scale; YMRS= Young Mania Rating Scale; FAST = Functioning Assessment Short Test; BIS = Barratt Impulsiveness Scale; TEMPS-A = Temperament Scale of Memphis, Pisa, Paris, and San Diego- Auto-questionnaire.

Table 2. Genotype distribution frequencies for early-onset and late-onset bipolar disorder.

SNP	Sample	N	Genotype Distribution n(f)			X^2	p
			CC	CA	AA		
***IMPA2*-rs669838**	Total	193	89 (.46)	77 (.40)	27 (.14)	0.133	0.93[a]
	EO	32	15 (.47)	12 (.38)	5 (.15)		
	LO	161	74 (.46)	65 (.40)	22 (.14)		
			GG	GA	AA		
***IMPA2*-rs1020294**	Total	195	85 (.44)	94 (.48)	16 (.08)	10.844	**0.01[a]**
	EO	32	9 (.28)	16 (.50)	7 (.22)		
	LO	163	76 (.47)	78 (.48)	9 (.05)		
			CC	CT	TT		

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***IMPA2*-rs1250171**	Total	194	93 (.48)	84 (.43)	17 (.09)	9.894	**0.01**[a]
	EO	32	21 (.65)	6 (.19)	5 (.16)		
	LO	162	72 (.45)	78 (.48)	12 (.07)		
			GG	GA	AA		
***IMPA2*-rs630110**	Total	194	90 (.46)	87 (.45)	17 (.09)	0.635	0.72[a]
	EO	32	17 (.53)	12 (.38)	3 (.09)		
	LO	162	73 (.45)	75 (.46)	14 (.09)		

Bold text in the table indicates significant values.
[a] Fisher's Exact Test.
EO= Early onset; LO= Late onset.

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Table 3. Allele distribution frequencies for early-onset and late-onset bipolar disorder.

SNP	Sample	N	Allele Distribution (f)		X^2	p
			C	A		
***IMPA2*-rs669838**	Total	193	255 (.66)	131 (.34)	0.007	1.0
	EO	32	42 (.66)	22 (.34)		
	LO	161	213 (.66)	109 (.34)		
			G	A		
***IMPA2*-rs1020294**	Total	195	264 (.68)	126 (.32)	7.961	**0.01**
	EO	32	34 (.52)	30 (.48)		
	LO	163	230 (.71)	96 (.29)		
			C	T		
***IMPA2*-rs1250171**	Total	194	270 (.70)	118 (.30)	1.061	0.37
	EO	32	48 (.75)	16 (.25)		
	LO	162	222 (.69)	102 (.31)		
			G	A		
***IMPA2*-rs630110**	Total	194	267 (.69)	121 (.31)	0.335	0.66
	EO	32	46 (.72)	18 (.28)		
	LO	162	221 (.68)	103 (.32)		

Bold text in the table indicates significant values.
EO= Early onset; LO= Late onset.

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Table 4. Binary logistic regression of predictor variables and late onset in bipolar disorder.

Predictors	B	Wald X^2	p	Odds ratio (OR)	95% CI for OR	
					Lower	Upper
Alcohol misuse	-1.625	8.613	**0.003**	0.197	0.066	0.583
Atypical symptoms	-0.783	2.284	0.131	0.457	0.166	1.262
G carriers–rs102094	2.258	10.051	**0.002**	9.565	2.368	38.638
T carriers-rs1250171	0.684	2.249	0.134	1.981	0.811	4.841
Rapid Cycling	0.061	0.012	0.914	1.063	0.353	3.203
Suicide Attempt	-0.120	0.064	0.800	0.887	0.349	2.250
Psychotic symptoms	-0.562	1.013	0.314	0.570	0.191	1.703

Bold text in the table indicates significant values.

Highlights:

- The age at onset of bipolar disorder has relevant clinical implications
- *IMPA2* genetic variations are seen in bipolar patients with early and late onset
- Defining subgroup of patients may increase diagnostic and therapeutical accuracy

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