SEROTONINERGIC AND DOPAMINERGIC GENES IN BIPOLAR DISORDER AND RESPONSE TO TREATMENTS IN BIPOLAR DEPRESSION. INVESTIGATION ON A WELL-CHARACTERIZED NATURALISTIC SAMPLE

Laura Mandelli, Marianna Mazza, Marco Di Nicola, Giovanni Martinotti, Daniela Tavian, Elisa Colombo, Sara Missaglia, Gloria Negri, Diana De Ronchi, Roberto Colombo, Luigi Janiri, Alessandro Serretti

Abstract

Inheritable factors are known to play an important role in the risk for Bipolar disorder (BD) as well as response to pharmacological treatment. In the present study, we further investigated four candidate genes for BD and response to pharmacological treatments, in a naturalistic sample of 131 patients and 65 healthy controls.

Patients were characterized for socio-demographic and clinical variables, including substance abuse, axis II personality disorders, temperamental traits and social adjustment. Patients meeting criteria for a depressive episode were followed for 6-months of pharmacological treatment (n=92). Polymorphisms within the genes for Serotonin receptor 2A (5HTR2A), trypthophan hydroxylase 1 (TPH1), Dopamine receptor D2 (DRD2) and Dopamine receptor D4 (DRD4), were analyzed for the present study. 5HTR2A, DRD2 and DRD4 variants were not associated to BD, response to treatment and other variables considered in the study. A haplotype in TPH1 (rs1800532-rs7933505) showed a trend of association with BD, though non-significantly considering correction for multiple testing.

Taking into account limitations linked to the small sample size and the naturalistic approach in recruitment and treatment of BD patients, this study does not support an involvement of the genes here considered in BD and medium-term outcome of bipolar depression. Further studies are required to clarify the role of TPH1, particularly of the less investigated rs7933505 variant in BD.

Key Words: gene, serotonin receptor 2A, tryptophan hydroxylase 1, dopamine receptor d2, dopamine receptor d4, bipolar disorder, treatment outcome

Declaration of interest: none

Laura Mandelli[1*], Marianna Mazza[2], Marco Di Nicola[2], Giovanni Martinotti[2], Daniela Tavian[3], Elisa Colombo[4], Sara Missaglia[4], Gloria Negri[4], Diana De Ronchi[1], Roberto Colombo[3,4], Luigi Janiri[2], Alessandro Serretti[1]

[1]Institute of Psychiatry, University of Bologna, Italy
[2]Department of Psychiatry and Psychology, Catholic University of Rome "A. Gemelli", Italy
[3]Laboratory of Human Molecular Biology and Genetics, Catholic University, Milan, Italy
[4]Institute of Biochemistry and Clinical biochemistry, Catholic University of Rome, Italy

Corresponding author
Laura Mandelli
University of Bologna, Institute of Psychiatry
V.le C. Pepoli 5, 40123 Bologna, Italy
E-mail: laura.mandelli@unibo.it

Introduction

Genetics play an important role in the risk for Bipolar disorder (BD) and response to specific treatments such as antidepressants and mood stabilizers. According to linkage studies, a number areas throughout the human genome have been repeatedly associated with BP and thus they represent "hot regions" (Barnett and Smoller 2009, Serretti and Mandelli 2008). Candidate genes, as located in these regions or encoding for factors hypothesized to be involved in the pathophysiology of mood disorder, have been also investigated in case-control, population and cohort studies. Consistent findings have been obtained for Brain derived neurotrophic factors (BDNF) (Fan and Sklar 2008), D-amino acid oxidase activator (DAOA) (Muller et al. 2011), Disrupted in schizophrenia 1 (DISC1) (Muir et al. 2008), Glutammate receptor ionotropic kainate 4 (GRIK4) (Blackwood et al. 2007, Pickard et al. 2006, Pickard et al. 2008), and the serotonin related genes Serotonin transporter (SLC6A4) (Mansour et al. 2005) and Tryptophan hydroxylase 2, neuronal (TPH2) (Barnett and Smoller 2009, Serretti and Mandelli 2008). Despite a large number of studies performed so far, only few consistent data have been obtained and mostly conflicting results are reported in literature. Besides diversity in the selection of genes and specific polymorphisms, methods of investigation and populations, the control of multiplex influences on complex traits represents a major challenge.

In order to take into account the heterogeneity and complexity of Bipolar disorder (BD), in 2007 we have

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started the recruitment of a naturalistic sample of bipolar-spectrum disorder patients, well-characterized for demographic and psychopathological features, comorbidities (particularly substance abuse disorders), personality, psychosocial adjustment and response to treatments over a period of 6-12-months. Despite recruitment is still proceeding and the sample is still undersized, early analyses have shown that the temperamental trait of harm Avoidance is a potential predictor of the medium/long term outcome of bipolar depression (Mandelli et al. in press) and moderates the effect of Serotonin transporter gene (5HTTLPR) (Mandelli et al. 2009). Further, we found an independent effect of the brain derived neurotrophic factor gene (BDNF) (Mandelli et al. 2010) and a significant association between the gene encoding for serotonin 2C receptor (5HTR2C) and BD (Mazza et al. 2010). In the present study, we preliminarily evaluated the role of four other candidate genes with both BD and the outcome bipolar depression. In particular, we focussed on two serotoninergic (serotonin receptor 2A, HTR2A and tryptophan hydroxylase 1, TPH1) and two dopaminergic genes (dopamine receptor D2, DRD2 and dopamine receptor D4, DRD4). HTR2A has been associated with many psychiatric disorders such as schizophrenia (Mowry and Nancarrow 2001), mood disorders (Choi et al. 2004, McAuley et al. 2009, Ranade et al. 2003), suicide (Arango et al. 2003), anxiety disorders (Domschke and Deckert 2010) and Alzheimer's disease (Norton and Owen 2005), but its' role in mood disorders remains controversial, particularly in BD and response to mood stabilizers (Serretti et al. 2007). After an initial positive report (Bellivier et al. 1998), mainly negative results have been instead reported with respect to TPH1 in BD (Chotai et al. 2005, Furlong et al. 1998, Lai et al. 2005, Rietschel et al. 2000, Serretti et al. 2001a, Vincent et al. 1999), though a recent positive meta-analysis has been published (Chen et al. 2008). However, we obtained early evidence on response to antidepressant treatment in previous independent samples (Serretti et al. 2001c, Serretti et al. 2004), though not replicated in Asiatic samples (Ham et al. 2005, Kato et al. 2007, Yoshida et al. 2002). In BD patients, we also observed a slight effect of TPH1 on the prophylactic efficacy of lithium (Serretti et al. 1999b). Dopamine receptor D4 gene (DRD4) is one of the genes most consistently associated with BD, though negative studies have also been published, while the gene coding for dopamine receptor D2 (DRD2) mainly received inconsistent findings (Serretti and Mandelli, 2008, Hayden and Nurnberger, 2006). These genes do not preliminarily seem to be involved in response to antidepressant treatments and lithium (Manchia et al. 2009, Serretti et al. 1999a), but further research is needed to confirm the findings.

Methods

In the present study we investigated 131 BD patients meeting DSM-IV criteria for BD type I (n=64, 48.9%) or BD type II (n=67, 51.1%), according to the Structured clinical interview for DSM-IV disorders, axis I (SCID-I) (First et al. 1990) and 65 healthy controls. Details of recruitment and evaluations have been previously described (Mazza et al. 2009). Out of 131 patients, 92 patients meet DSM-IV criteria for a major depressive episode (SCID-I) and were entered in a 6-months follow-up and evaluated for depressive severity at baseline and after 1, 3 and 6 months by the Hamilton scale for depression (HRSD) (Hamilton 1960). Patients underwent a naturalistic treatment, with mood stabilizers and new antiepileptic drugs, antidepressants, conventional antipsychotics and atypical antipsychotics. Antidepressant equivalents were calculated according to the Antidepressant Treatment History form (Sackeim et al. 1990). The Institutional Review Board approved the study; written informed consent was asked after a complete description of the study was provided to each subject. Genetic analyses were performed according to standardized protocols. Four SNPs were analyzed for 5HTR2A (rs6311, rs6313, rs1928040 and rs7997012) (Kishi et al. 2009), 2 in TPH1 (rs1800532 and rs7933505) (Andreou et al. in press, Serretti et al. 2001a), 2 in DRD2 (-141C ins/del and rs1800497) (Dolzan et al. 2007, Noble et al. 1994) and 2 in DRD4 (Ronai et al. 2001, Serretti et al. 1998), according to standardized procedures. Alleles for the 48bp VNTR in DRD4 were clustered in long and short as previously reported (Serretti et al. 2001b). Statistical linear analyses were performed by the Pearson correlation, chi-square test, Student t-test and one-way analysis of variance (ANOVA) when appropriate. The association analysis with depressive severity over time was performed by the repeated-measure ANCOVA controlling for baseline severity, treatment type and antidepressant equivalents. The haploview software (http://www.broadinstitute.org/haploview) was employed to calculate the Hardy-Weinberg equilibrium for each polymorphism, linkage disequilibrium among polymorphisms in the same gene and to perform simple allelic and haplotypes association with BD. Haplotypes were further analyzed by the R software (http://www.r-project.org/) for both association with BD and response to treatments for bipolar depression. The False discovery rate (FDR) procedure was employed to identify reliable significance considering multiple testing, separately in case-control associations and response to treatments. All the analyses were two tailed with an alpha value of 0.05. With these parameters, in our sample we had a sufficient power of 0.80 to detect small-medium effect sizes (w=0.22) in case-control associations and small effect sizes (f=0.10) in association with response to treatments (3 groups for 4 repetitions).

Results

All genotypes were in HWE equilibrium in the whole sample; two SNPs in 5HTR2A were in Linkage disequilibrium (rs6313 and rs1928040, D'=0.85, LOD=43.6 r^2=0.65), as well as the two SNPs in TPH1 (D'=0.96 LOD=72.6 r^2=0.92). Similar results were obtained separately in cases and controls (data available on request). Genotypes were not differentially stratified in BD patients and controls, except for a small trend regarding TPH1 genotypes (**table 1**). The C alleles in both TPH1 markers showed trends of association with BD (allelic analysis, p=0.026 for both polymorphisms) and the C-C haplotype was slightly more frequent in

Table 1. *Distribution of genotypes in controls and BD patients*

	Genotypes	Controls N(%)	BD patients N(%)	Chi-sq	P
		5HTR2A			
Rs6311	AA	19(33.93)	37(66.07)	1.65	0.44
	AG	32(36.78)	55(63.22)		
	GG	14(26.42)	39(73.58)		
Rs6313	TT	20(35.71)	36(64.29)	1.53	0.46
	TC	31(35.63)	56(64.37)		
	CC	14(26.42)	39(73.58)		
Rs1928040	TT	18(29.03)	44(70.97)	0.81	0.67
	TC	31(36.05)	55(63.95)		
	CC	16(33.33)	32(66.67)		
Rs7997012	CC	29(33.72)	57(66.28)	0.35	0.84
	CT	28(31.46)	61(68.54)		
	TT	8(38.10)	13(61.90)		
		TPH1			
Rs1800532	CC	18(26.87)	49(73.13)		
	CA	28(31.11)	62(68.89)		
	AA	19(48.72)	20(51.28)	5.43	0.07
Rs7933505	CC	17(26.15)	48(73.85)		
	CT	30(31.91)	64(68.09)		
	TT	18(48.65)	19(51.35)	5.35	0.07
		DRD2			
-141C ins/del	Ins/Ins	60(33.71)	118(66.29)	0.94	0.62
	Ins/Del	5(29.41)	12(70.59)		
	Del/Del	0(0.00)	1(100.00)		
Rs1800497	TT	39(29.77)	92(70.23)	2.08	0.35
	TC	25(40.32)	37(59.68)		
	CC	1(33.33)	2(66.67)		
		DRD4			
Rs1800955	TT	16(27.59)	42(72.41)	2.19	0.33
	TC	37(38.14)	60(61.86)		
	CC	12(29.27)	29(70.73)		
48bp VNTR	S/S	47(34.56)	89(65.44)	0.98	0.61
	S/L	15(28.30)	38(71.70)		
	L/L	3(42.86)	4(57.14)		

LEGEND: BD – bipolar disorder, 5HTR2 - serotonin receptor 2A, TPH1 - trypthophan hydroxilase 1, DRD2 - dopamine receptor 2, DRD - dopamine receptor 4

Table2. *Distribution of THP1 haplotypes in controls and BD patients*

THP 1 Haplotypes	Freq. tot	Freq. in Controls	Freq. in BD patients	Chi-sq	p
C-C	0.56	0.48	0.60	5.61	0.018
T-A	0.42	0.49	0.38	4.37	0.037
T-C	0.01	0.015	0.008	0.51	0.47
C-A	0.01	0.015	0.008	0.51	0.47

LEGEND: BD – bipolar disorder, THP1 - thrypthophan hydroxilase 1

Table 3. *Repeated measures of ANOVA on course of symptoms over 6 months of treatment covaring for baseline severity*

	$F_{(df=2, 140)}$, p
5HTR2A	
rs6311	1.03, 0.39
rs6313	1.42, 0.23
rs1928040	0.68, 0.61
rs7997012	0.89, 0.47
TPH1	
rs1800532	1.34, 0.26
rs7933505	1.24, 0.30
DRD2	
-141C ins/del	0.09, 1.00
rs1800497	2.05, 0.09
DRD4	
rs1800955	0.78, 0.54
48bp VNTR	1.29, 0.28

LEGEND: 5HTR2A - serotonin receptor 2A, TPH1 - thrypthophan hydroxilase 1, DRD2 - dopamine receptor 2, DRD4 - dopamine receptor 4

cases than in controls (**table 2**). Nevertheless, these associations were not significant considering correction for multiple testing (required alpha <0.005). In the sub-sample of 92 depressed patients, variables independently associated with a worse depressive outcome after controlling for their reciprocal correlations were: female sex (F=4.73 df=3,192 p=0.003), high HA (F=3.59 df=3,192 p=0.015) and depressive severity at baseline (F=9.73 df=13,192 p=0.00005). In this sample, neither single markers nor haplotypes (5HTR2A and TPH1) were differentially stratified for any demographic and clinical features considered, including baseline severity, gender and HA. No marker or haplotype was significantly associated with the course of symptoms over time, before and after controlling for potential confounders (**table 3**).

Discussion

Overall, the present study does not confirm previous reported associations with genes here considered and BD, though comparison with previous studies is problematic, since the "naturalistic" approach in the recruitment and treatment of patients. In detail, we were not able to replicate the reported association between the 5HTR2A promoter polymorphism rs6311and BD (Bonnier et al. 2002, Chee et al. 2001), though, overall, the 5HTR2A gene has received many inconsistent findings in BD (Serretti and Mandelli 2008). In a previous studies, we found a small effect of rs3613 on response to antidepressants in both major depressives and BD patients (Cusin et al. 2002), though no association with prophylactic efficacy of lithium (Serretti et al. 2000). In this sample, no effect of 5HTR2A was observed on bipolar depression outcome, also controlling for the type of treatment administered and antidepressant equivalents. Similarly, negative findings were obtained for both DRD2 and DRD4 variants. While the negative effect of DRD2 is consistent with a large part of the existing literature, the lack of association between DRD4 and BD is not consistent, since DRD4 has been repeatedly associated to BD, particularly in studies that focussed the 48bp VNTR polymorphism in exon 3 (see Serretti and Mandelli 2008). As regards the response to treatments, in previous studies, polymorphisms in both DRD2 and DRD4 were not find associated to acute and prophylactic treatment with lithium in two independent studies (Manchia et al. 2009, Serretti et al. 1999a), suggesting no effect of these genes, at least as regards lithium treatment. As a main finding in this study, we found a slight trend of difference in the distribution of two common haplotypes in TPH1 in BD patients and controls. Previous studies have mainly focussed on the rs1800532 (+218C/A) polymorphism in intron 7 and most of them reported no association with BD (see Serretti and Mandelli 2008). We here focussed on the same polymorphism together with another in the same intron 7 (rs7933505), previously associated with major depression (Gizatullin et al. 2006) and, recently, to schizophrenia (Saetre et al. 2010). Therefore, rs7933505 may play an important role in BD as well, but further studies are required to confirm this preliminary finding. Similarly to other genes, only few studies investigated TPH1 in response to treatments in BD. In previous studies, we found rs1800532 slightly associated with response to prophylactic treatment with lithium (Serretti et al. 1999b) and antidepressant augmentation with pindolol (Serretti et al. 2001c). In this study, we could not observe any effect of THP1 variants on the outcome of bipolar depression. Further studies are thus required to clarify the role of TPH1 in response to treatments for BD. Results from our study should be viewed in light of a number of limitations, the specific composition of our sample and the naturalistic prospective study's design. Major limitations of our study are represented by the small sample size and the naturalistic approach that we employed for the recruitment and treatment of patients, though we opted intentionally for this approach in order to consider the effect of multiple variables. Notwithstanding, unlike previous studies, just few exclusion criteria were considered and both patients affected by BD type I and II were included, as well as patients with comorbid disorders such as substance abuse and axis II personality disorders. A cut-off of depressive severity for inclusion (for example HDRS>15) was not employed, but only a diagnosis of depressive episode according DSM-IV criteria was considered for inclusion in the study. Patients did not receive a single standardized treatment and the length of follow-up was considerably longer than most of the studies, which are usually limited to the acute treatment over 6-8 weeks.

In conclusion, data from our study do not add evidence of an involvement of the genes here considered in BD and in the outcome of bipolar depression under pharmacological treatment. As a trend, we observed a potential involvement of TPH1 in the risk for BD when

considering the haplotype composed by polymorphisms rs1800532 and rs7933505. Nevertheless, this effect did not survive correction for multiple testing and, given the high risk for false positive associations in our study, it has to be taken with caution.

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