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# Euthymic and depressed bipolar patients are characterized by different RNA editing patterns in blood

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## ABSTRACT

Bipolar disorder (BD) is a worldwide leading cause of disability. Inflammation roles in this disease is well established. *ADAR1*-mediated RNA editing is one of the key mechanisms regulating the inflammatory response. We have identified a panel of RNA editing-based blood biomarkers which allowed to discriminate unipolar from BD depression with high accuracy. We confirmed here the diagnostic value of this panel in a new cohort of BD patients recruited in Brazil. We also identified new combinations which allow a clear discrimination of BD from healthy controls and among BD subgroups, confirming that RNA editing is a key mechanism in BD.

## 1. Introduction

Bipolar disorder (BD) is a mental illness characterized by mood swings between depressive and hypomanic or manic episodes (Merikangas et al., 2011; Carvalho et al., 2020a, 2020b), which can lead to functional impairment, high disability, and premature mortality due to medical comorbidities such as diabetes, metabolic syndrome, or cardiovascular disease (Huang et al., 2021; Vadodaria et al., 2021).

RNA editing is a crucial mechanism that prevents autoimmunity by regulating the innate immune system and inflammatory response (Lamers et al., 2019; Ahmad et al., 2021). *ADAR1* is an important RNA editing enzyme that mediates RNA editing (Mannion et al., 2014; Lamers et al., 2019). RNA editing of synapse-associated proteins and of other key proteins for nervous system activity can modulate neurotransmission and affect behaviors, such as locomotion and depression (Berg et al., 2001; Rosenthal and Seeburg, 2012). Recent studies have identified modifications in mRNA editing of *HTR2c* and *PDE8A* genes in depressed individuals and suicide attempters (Chimienti et al., 2019; Weissmann et al., 2016) and demonstrated the diagnostic value of RNA editing as marker in depression, in interferon treated hepatitis C virus

(HCV) patients, and in depressed patients and suicide attempters compared to healthy controls (Salvetat et al., 2019, 2021). A panel of eight RNA editing-based blood biomarkers, including *PDE8A*, *CAMK1D*, *GAB2*, *IFNAR1*, *KCNJ15*, *LYN*, *MDM2*, and *PRKCB*, was identified to diagnose BD with high sensitivity and specificity (Salvetat et al., 2022). In the present study, we tested the diagnostic value of this panel for BD in a group of patients from a well-known genetic admixed ancestry population from Brazil (Galisa et al., 2022; Lezirovitz and Mingroni-Netto, 2022). New combinations were identified that can distinguish euthymic from depressed bipolar patients, euthymic from manic-bipolar patients, and euthymic from healthy controls.

## 2. Material and method

More informations about materials and methods was described in Salvetat et al. (2022).

### 2.1. Subjects and clinical assessment

This study was approved by the Research Ethics Committee of

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UNIFESP [CEP No. 1427/16], and all participants gave a written informed consent. Eligible participants, males and females, aged from 18 to 60 years, underwent the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-1). Manic and depressive symptoms severity was assessed using the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale-17 items (HDRS). Global Assessment of Functioning (GAF) scores was assessed in the dual-scale system aiming to describe both symptoms and functional impairment (Pedersen and Karterud, 2012). Patients followed a stable medication regimen, defined as receiving the same medications at consistent doses for a minimum of two months prior to study inclusion, primarily mood stabilizers, with some on antipsychotics or benzodiazepines. The healthy control (CTRL) group consisted of volunteers who had no current or lifetime mental disorders, no history of being prescribed psychotropic medications, and had negative family history of a major psychiatric disorder. Euthymic patients were selected with HDRS and YMRS scores of 8 or less to minimize the bias of symptomatology on psychosocial functioning (Bonnin et al., 2010; Rosa et al., 2010). The exclusion criteria for all groups were acute and chronic general medical conditions, recent use of anti-hypertensive medication, pregnancy and breastfeeding. The study strictly adhered to the principles expressed in the Declaration of Helsinki.

## 2.2. RNA extraction and qualification

Samples were retrieved in PAXgene™ blood RNA tubes and extracted using MagNA Pure 96 instrument (Roche). Total RNA concentrations and quality were determined with Qubit Fluorometer (Invitrogen) and LabChip (Perkin-Elmer) instruments, respectively. Samples with RNA integrity values > 7 were used for further analysis.

## 2.3. Targeted next generation sequencing

Each gene were amplified with validated primers on a Pqstar 96 × thermocycler (Biorad). PCR products were purified with magnetic beads, quantified and indexed. The library was pooled, purified, denatured, spiked with PhiX Control V3 and loaded onto a sequencing cartridge according to manufacture guidelines, and for finally being sequenced at standard concentrations using Illumina NextSeq 500.

## 2.4. Bioinformatics analysis

The sequencing data obtained were checked for quality using FastQC software. A pretreatment step consisting of filtering off the sequences according to length and quality score was performed. The processed reads were aligned to the reference human genome sequence GRCh38 using bowtie2 (Langmead and Salzberg, 2012). SAMtools mpileup (Li, 2011) was used for SVN calling. The edited positions in the alignment were identified using in-house scripts, which counted the number of different nucleotides in each genomic location. The percentage of all possible sites or isoforms of each transcript was computed, and a relative proportion of at least 0.5% was set as minimal value.

## 2.5. Statistical analysis

All statistics and figures were computed with the "R/Bioconductor" software (Gentleman et al., 2004; R Core Team, 2005). A "Target Editing Index" (TEI), resuming gene-specific editing values, was computed by linear combination of significant RNA editing variants which maximizes the AUC ROC (Su and Liu, 1993; Staack et al., 2006). The TEI was transformed using Boxcox transform (Box and Cox, 1964) aiming to guarantee the normal distribution of data. A differential analysis was performed using Student's *t*-test. The Benjamini and Hochberg (BH) procedure (Benjamini and Hochberg, 1995) was applied to control the false discovery rate (FDR) and an adjusted *p*-value below 0.05 was considered as statistically significant.

## 3. Results

### 3.1. Patients characteristics

This study analyzed 47 control patients (CTRL) compared to 40 patients with bipolar disorder (BD). BD patients were classified into 4 subgroups: euthymic (BD\_EUT, *n* = 17), depressive (BD\_DEP, *n* = 11), manic/hypomanic (BD\_HM/M, *n* = 7) and mixed (BD\_MIX, *n* = 5). As shown in Supplementary Table 1, their characterization corresponded to the application of different clinical rating scales.

### 3.2. Differential editing analyses

Four independent differential analyses were performed, based on the RNA editing values observed for each of the 8 targeted genes, and resumed in a "Target Editing Index" (TEI). The CTRL group was compared to BD group, BD\_EUT group, BD\_DEP group, or BD\_HM/M group. BD patients and BD\_EUT showed higher levels of edited RNA on *CAMK1D*, *GAB2*, *MDM2*, *PDE8A* and *PRKCB* genes. BD\_DEP and BD\_HM/M patients showed higher levels of edited RNA on *IFNAR1*, *MDM2*, *PRKCB* and *LYN* (Fig. 1A, Supplementary Figures S1-S6).

### 3.3. Combination analysis

Significant editing sites and/or isoforms were selected and combined with each other to identify the best combination for each comparison and to allow separation of subgroups of BD patients.

As shown in Fig. 1B, a combination (Z1) of 19 selected RNA editing biomarkers (BMs) resulted in an AUC of 0.887, with a sensitivity of 85% and a specificity of 89.4%, therefore with a clear separation of BD from CTRL.

As shown in Fig. 1C, 3 different biomarkers combinations (Z2: CTRL vs BD\_EUT with 29 BMs, Z3: CTRL vs BD\_DEP with 12 BMs, Z4: BD\_DEP vs BD\_EUT with 16BMs) leading to an AUC ROC value of 0.996, 0.938, 0.993 respectively, allowed a stringent separation of 3 groups: CTRL, BD\_EUT and BD\_DEP.

Two other biomarkers combinations (Z5: CTRL vs BD\_HM/M with 6 BMs and Z6:BD\_EUT vs BD\_HM with 9 BMs) leading to an AUC ROC value of 0.993 and 0.971 respectively, which associated with Z2 combination allowed a clear separation of 3 other groups: CTRL, BD\_EUT and BD\_HM/M (Fig. 1D).

## 4. Discussion

The value of blood biomarkers in BD, including neurotrophins alterations, increased inflammatory and oxidative stress, and elevated cytokines during manic and depressive phases has been suggested (Walz et al., 2007; Munkholm et al., 2014; Sayana et al., 2017) but clinical validation is still lacking. In a previous study, we have described a panel of 8 blood RNA editing-based biomarkers to differentiate unipolar and bipolar depressed patients, aiding clinical management (Salvetat et al., 2022). The present study showed the diagnostic value of these 8 edited genes in differentiating subgroups of BD patients. Despite the relative small sample size, these BD patients were clinically well-characterized with psychological scales. Some limitations must be considered: First, bipolar patients were older (mean:45 years old) than control participants (mean:35 years old), which may have biased the performance of the algorithm. Second, we cannot exclude that a small number of RNA editing biomarkers in our panel may be linked to medication rather than disease status due to limited patient numbers in stratified analysis, making refined control challenging. The observed differences in RNA editing between BP\_EUT and BP\_DEP could be interpreted as a signature of treatment response rather than due to pathology. However, the significant difference between CTRL and BP\_EUT shows that RNA editing biomarker combination signs the pathology. Modulating ADAR activity may also enhance the effectiveness of psychiatric treatments. This

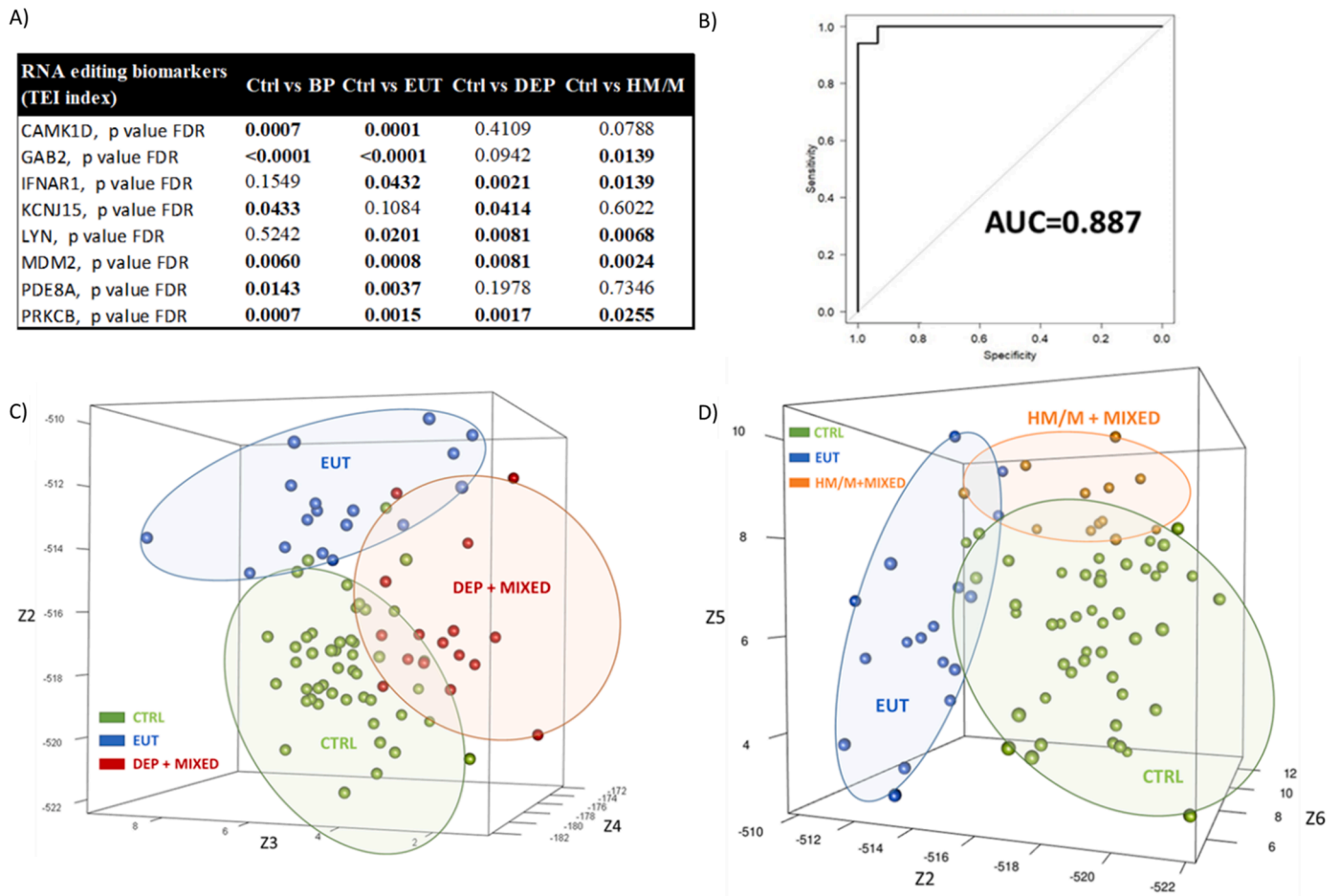


Fig. 1. RNA editing biomarkers combination for discriminate CTRL vs BD patients.

A) Differential RNA editing analyses of participants.

B) ROC curves of the RNA editing biomarkers combination for CTRL vs BD.

C) Scatterplot 3D of the best combination for discriminate CTRL vs EUT vs DEP\_MIXED subgroups.

D) Scatterplot 3D of the best combination for discriminate CTRL vs EUT vs HM/M\_MIXED subgroups.

approach is currently being tested in cancer therapy, where ADAR inhibitors are combined with chemotherapy or immunotherapy treatments to improve their efficacy (Bhate et al., 2019; Ishizuka et al., 2019; Tusup et al., 2021). The present study highlights RNA editing as a key mechanism in the pathophysiology of mental disorders, and particularly in BD. Thus, measuring changes in RNA editing at the peripheral level, allowed us to stratify BD patients, not only with respect to their symptomatology but also with respect to the pathophysiology, thus paving the way for personalized medicine in psychiatry.

#### Ethical statement

I testify on behalf of all co-authors that our article:

This material has not been published in whole or in part elsewhere. The manuscript is not currently being considered for publication in another journal, and all authors have been personally and actively involved in substantive work leading to the manuscript and will hold themselves jointly and individually responsible for its content.

#### Declaration of Competing Interest

The authors declare no conflicts of interest.

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#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2023.115422](https://doi.org/10.1016/j.psychres.2023.115422).

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