

Leukocyte telomere length significantly correlates with duration of lithium treatment in bipolar disorder patients

C. Pisanu¹, G. Baggiani², D. Congiu¹, C. Melis¹, P. Niola¹, P. Caria³, G. Severino¹, C. Chillotti², R. Vanni³, A. Bocchetta², M. Del Zompo^{1,2}, A. Squassina¹

¹Dept. of Biomedical Sciences, Section of Neuroscience and Clinical Pharmacology, University of Cagliari, Italy

²Unit of Clinical Pharmacology of the University Hospital of Cagliari, Italy

³Dept. of Biomedical Sciences, University of Cagliari, Italy

Bipolar disorder (BD) is a disabling psychiatric disease characterized by alternating episodes of mania and depression. Lithium represents the mainstay in the maintenance of BD, but its mechanism of action is still far from being completely elucidated. Several studies reported premature cell senescence in BD, as shown by reduced telomere length in affected subjects. Recent findings have also shown that antidepressants and lithium may have a protective effect against telomere shortening. In this study, we sought to investigate the correlation between leukocytes telomere length (LTL) and clinical response to long-term lithium treatment in BD. The sample comprised 200 patients of Sardinian ancestry with BD diagnosed according to DSM-IV and SADS-L criteria. Number of manic and depressive episodes, duration of lithium treatment and number of suicide attempts were also assessed. Patients were characterized for lithium response using the 'Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder' as described previously (Grof et al., 2002). DNA was extracted from leukocytes and relative LTL assessed using SYBR Green real-time PCR as described in Cawthon (2002). A control sample (calibrator) was included in each plate and LTL was calculated using the 2e-DDCT method. Correlation between LTL and age was assessed using nonparametric Spearman's correlation test. Correlation between LTL and duration of lithium treatment was determined using the partial correlation test, controlled for age. The effect of duration of lithium treatment, number of suicide attempts, number of depressive and manic episodes on LTL was assessed using the linear regression test, controlled for age. Dependence of LTL on diagnosis or response to lithium treatment was tested using analysis of covariance (ANCOVA), adjusted for age. A P-value < 0.05 was considered as statistically significant.

LTL correlated negatively with age ($P = 0.0002$, Spearman's $\rho = -0.256$) and was independent of sex ($p > 0.05$). There was a trend for a longer LTL in BD I patients compared to BD II patients, although not statistically significant ($P = 0.062$). Interestingly, LTL correlated positively with lithium treatment duration in patients with a duration of lithium treatment above 24 months ($n = 150$, $p = 0.037$, Spearman's $\rho = 0.171$) and was positively dependent on lithium treatment duration (lithium treatment duration: standardized coefficient = 0.175, $t = 2.107$, $p = 0.037$; age: standardized coefficient = -0.251; $t = -3.027$, $p = 0.003$; $R^2 = 0.069$). LTL was not dependent on lithium response, number of suicide attempts and number of depressive or manic episodes, after adjusting for age.

Our data support previous findings showing that long-term lithium treatment has a protective effect against telomere shortening in BD patients, though in our study this effect appeared to be independent from lithium clinical efficacy.

Grof P et al. (2002). *J Clin Psychiatry*. 63: 942–947.

Cawthon RM (2002). *Nucleic Acids Res*. 30(10):e47