Biomarkers in Mononuclear Blood Cells for Lithium Treatment Response of Bipolar Disorder

NCT02909504

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STUDY DESIGN AND OBJECTIVES:

Study Design: This study is a 4-month open-label study of lithium in the acute treatment of patients with bipolar I or II disorder. Eligible patients will receive lithium 300 mg twice daily and titrated in 300 mg increments every 7 days as tolerated to levels $\geq$ 0.6 mEq/L. Blood samples are collected at baseline and at the end of study. Analyses of 45 molecule expressions in mononuclear blood cells at baseline and endpoint will be carried out after the completion of study (see Appendix). Fifty patients meeting DSM-5 criteria for bipolar I or II will be enrolled.

Patients will be seen within the Mood Disorders Program at University Hospitals Cleveland Medical Center, 10524 Euclid Avenue, 12th Floor, Cleveland, Ohio 44106. Assessments will be performed by highly trained research assistants and psychiatrists, and required lab specimens will be collected by a phlebotomist in the Department of Psychiatry and analyzed at the Laboratory of University Hospitals Cleveland Medical Center for routine chemistry, and the laboratory of Dr. David Kaplan, MD, PhD. of CellPrint Biotechnology, 11000 Cedar Road, Suite 265, Cleveland, OH, 44106, for potential biomarkers. Dr. Kaplan, the founder of CellPrint Biotechnology, is the Co-Principal Investigator of this project.

Primary Objectives: The primary objective of this study is to identify biomarkers that illuminate the lithium response in patients with bipolar disorder.

Hypothesis 1: Changes in molecular expression after lithium treatment differ between responders and non-responders. Molecular differences between the two patient classes will help reveal the underlying mechanism of lithium response.

Hypothesis 2: Molecular expression patterns can be used to predict response or non-response to lithium treatment. Ideally, the molecular expression pattern will also vary between responsive and non-responsive patients *before* treatment. Since blood samples are easily obtained, the study has the potential to change the landscape of using blood to study molecular changes in patients with bipolar disorder or other psychiatric disorders.

Study Design
The study consists of 2 stages: screening phase and treatment phase (See Table 1 below).

Screening Phase: The Screening phase is up to 4 weeks in duration. Patients will sign the informed consent form, and then be evaluated by the clinician. Diagnoses will be confirmed by the MINI for DSM-5 (Mini International Neuropsychiatric Interview for DSM-5). A medical history and physical exam (H&P) will be completed, along with laboratory testing.

Treatment Phase: Eligible patients will receive lithium treatment at Baseline (Visit 2). Any psychotropic medications (with the exception of allowed rescue medications) will be tapered off by week 4. The study psychiatrist will work with an individual participant concerning how quickly and to what schedule the prohibited medication(s) will be weaned off. Participants will be closely monitored, and will come in for unscheduled visits if necessary (typically 1 visit per week, though can be as frequent as required), and will be encouraged to contact the clinic if they have questions or concerns. The participant will be discontinued from the trial if their mood worsens to a significant degree and/or they cannot discontinue excluded concomitant medication(s).

TARGET STUDY POPULATION

Inclusion Criteria

For inclusion in this study, subjects must meet all of the following criteria:

1) Able to provide informed consent before beginning any study-specific procedures;
2) Male or female, 18-70 years old;
3) Meets current DSM-5 criteria for bipolar I or II disorder as assessed by the MINI;
4) Any symptomatic phase of bipolar I or II disorder including, depressive, manic, mixed or hypomanic
5) Global Clinical Impression-Severity for Bipolar Disorder (CGI-S-BD) ≥3;
6) Willing to take lithium;
7) If a sexually active female of childbearing potential, be using a double barrier method of contraception for the duration of the study;
8) Women with reproductive potential must have a negative urine pregnancy test;
9) Willing to have blood drawn:

Exclusion Criteria

Any of the following is regarded as a criterion for exclusion from the study:

1) Unwilling to comply with study requirements;
2) Renal impairment (serum creatinine >1.5 mg/dL);
3) Thyroid stimulating hormone (TSH) over >20% above the upper normal limit (participants maintained on thyroid medication must be euthyroid for at least 3 months before Visit 1;
4) Other contraindication to lithium,
5) Patients who have had severe adverse reaction to Lithium;
6) Patients who require inpatient care;
7) Drug/alcohol dependence requiring immediate acute detoxification;
8) Pregnancy as determined by serum pregnancy test or breastfeeding;
9) History of nonresponse to lithium at doses ≥ 900 mg/d for ≥ 8 weeks;
10) Unwilling to have blood drawn
11) Patients with chronic medical conditions such as diabetes, coronary artery disease, immune diseases, infectious diseases and neurological disorders;
12) Active suicidal ideation with a plan or intent, a suicide attempt within past 6 months or more than 2 suicide attempts within the past 2 years.
13) Currently on lithium

STUDY SPECIFIC PROCEDURES

After obtaining the informed consent, all potential research participants will be assessed with a systemic clinical interview and a structured interview with MINI. For those who meet the diagnostic inclusion criteria, psychiatric assessments will be administered. All eligible participants will also complete a Clinical Record Form. The form includes demographics (including date of birth, sex, race, and ethnicity), previous treatment history, the number of previous episodes, family history, and other historical correlates.

Medical History: Medical history includes current and previous history of disease(s) related to all body systems, diabetes mellitus risk factors, and other cardiovascular disease risk factors such as the Framingham Risk Score (FRS) which will be assessed by a sex-specific algorithm developed by D'Agostino (2008) and Wilson (2007) respectively, based on the Framingham Study. The updated

FRS enables identification of risk for any and all initial atherosclerotic cardiovascular disease events and is ideally designed for primary care (D'Agostino et al., 2008).

Prior and Current Medications: including medication name, dose, frequency, and duration.

Adverse Events (Side Effects): including duration, severity and outcome.

MINI-for DSM-5: Mini-International Neuropsychiatric Interview-for DSM-5: Diagnostic evaluation tool done at screening to ensure the participant is eligible for the protocol. This version accounts for current diagnoses.

CIRS: (Cumulative Illness Rating Scale, Linn et al., 1968): used to assess overall well-being both physically and mentally.

TLFB: The Timeline Follow back procedure for substance use completed by the research coordinator in all participants regardless of whether they meet the DSM-5 criteria for a substance use disorder.

Side Effects/Safety Measure:

a. FIBSR/GRSEB: Frequency, Intensity, and Burden of Side Effects Ratings/Global Rating of Side Effects Burden is a 3-item self-rated measure of medication side effects including intensity, frequency, and impairment.
b. C-SSRS: Columbia Suicide-Severity Rating Scale (Posner et al 2007) will be used to monitor the safety and side effects.

Severity Scales: Current symptom severity will be assessed using the following:

a. Clinical Global Impression-Severity for Bipolar Disorder (CGI-S-BD, Spearing et al., 2007) will be used to measure the overall bipolar illness severity.
b. CGI-EI: Clinical Global Impression-Efficacy Index: The CGI-EI integrates rated benefit and harms to yield scores that can be compared across interventions [Guy, 1976]. Thus, the CGI-EI provides a ratio of benefit to harm that reflects overall therapeutic effects in relationship to side effects. Therapeutic Effects are rated between 1 (unchanged or worse) and 4 (complete or nearly complete remission of all symptoms). Side Effects are also rated between 1 (none) and 4 (outweigh therapeutic effect). CGI-EI scores are ratios of Therapeutic Effects/Side Effects, and thus range from 0.25 (=1/4) to 4.00 (=4/1), with higher ratings representing more favorable benefit/harm ratios.
c. Montgomery Depression Rating Scale (MADRS, Montgomery & Asberg 1979) will be used to measure the severity of depression. It has become a standard rating scale in bipolar depression studies.
d. 16 Quick Inventory of Depression Symptomatology-Self Report (QIDS-SR16, Rush et al., 2003) will also be used to measure depression severity. This self-reported questionnaire was developed based on the DSM-V diagnostic criteria for a major depressive disorder episode.
e. Young Mania Rating Scale (YMRS, Young et al., 1978) will be used to measure manic symptoms severity
f. Hamilton anxiety score (HAM-A, Hamilton, 1959) will be used to measure anxiety severity.
g. Snaith-Hamilton Pleasure Scale (SHAPS, Snaith et al., 1995) will be used to assess feelings of anhedonia.

Functional Impairment and Quality of Life: Functional impairment and quality of life will be assessed using the following:

a. SDS (Sheehan Disability Scale, Leon et al., 1997) will be used to measure disability and impairment.
b. Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF, Endicott et al., 1991) will be used to measure of the degree of enjoyment and satisfaction in various areas of daily living.
c. Iowa Fatigue Scale (IFS) will be used to measure the severity of fatigue.

Physical and Laboratory Monitoring: Vital signs, weight, and waist circumference will be recorded at all study visits and height will be assessed at screening. A urine pregnancy test will be completed at screening and end of study for all women of childbearing potential. If a female participant has a positive urine pregnancy test at screening, they will be excluded from participating. A blood draw of approximately 3 teaspoons will be obtained from all patients at screening and end of study to measure CBC w/ diff, Comprehensive Metabolic Panel (including electrolytes, kidney function and liver function), and TSH and an additional 1 teaspoon of blood will be drawn for the analyses done by CellPrint Biotechnology. Lithium levels will be drawn as needed during the study and at end of study, with each draw containing approximately 1 teaspoon of blood. The labs will be drawn by a phlebotomist at University Hospitals and analyzed at University Hospitals Laboratory Services Foundation and results of test will be reviewed by a study doctor.

Patients may return to the site any time their condition warrants medical attention. At these Unscheduled Visits, study related procedures may be performed at the discretion of the investigator. Unscheduled Visits should not replace scheduled visits for the patient. Otherwise, all scheduled visits and corresponding assessments to be completed can be found in Table 1.

STUDY DRUG AND DOSING:
Lithium will be initiated at 300 mg per day for 3 nights and then increased to 600 mg/d as tolerated. After at least 5 days of treatment with lithium 600 mg/d, a lithium level will be done. If necessary, titration in 300 mg increments every 7days as tolerated will take place to achieve blood lithium levels $\geq$ 0.6mEq/L. This routine will require the investigator to titrate Lithium to whatever is maximally tolerated without any side effects, not just 0.6. If adverse effects occur, the dose will be decreased. The titration scheme ensures that patients receive the highest possible dose while not experiencing side effects that would compromise retention (Hopkins & Gelenberg, 2000) and has been in place since 1985 when the NIMH Consensus Development Conference issued this recommendation. If subjects do not tolerate at least 600mg/d, they may be discontinued.

Table 1: Flow Chart of the Study

	Screening	Baseline	Lithium Treatment Phase							End of Study***
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
Weeks		**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	
Consent	X									
MINI- DSM-5	X									
H&P	X									X
CIRS	X									X
CBC w/ diff	X									X
CMP	X									X
TSH	X									X
Urine Pregnancy	X									X
Lithium level*			X							X
Cell Biomarkers	X									X
ECG**	X									
Vitals	X	X	X	X	X	X	X	X	X	
MADRS		X	X	X	X	X	X	X	X	
YMRS		X	X	X	X	X	X	X	X	
HAMA		X	X	X	X	X	X	X	X	
QIDS-SR16	X	X	X	X	X	X	X	X	X	
CGI-S-BP	X	X	X	X	X	X	X	X	X	
CGI-EI			X	X	X	X	X	X	X	
SDS		X	X	X	X	X	X	X	X	
FIBSR		X	X	X	X	X	X	X	X	
Q-LES-Q-SF		X	X	X	X	X	X	X	X	
C-SSRS		X				X			X	
FRS		X	X	X	X	X	X	X	X	
IFS		X	X	X	X	X	X	X	X	
TLFB		X	X	X	X	X	X	X	X	
Physician Visit	X	X	X	X	X	X	X	X	X	X
Adverse Events (Side effects)			X	X	X	X	X	X	X	X
Medication History/Con Meds	X	X	X	X	X	X	X	X	X	X

* PRN
** If clinically indicated
*** End of Study: these assessments in addition to the visit the subject is attending

Criteria for study discontinuation:
Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient from this study are, but not limited to:

- Voluntary discontinuation by the subject who are at any time free to discontinue their participation in the study, without prejudice to further treatment;

- Safety reasons as judged by the investigator, particularly a clinically significant or serious adverse event that would not be consistent with continuation in the study or an imminent risk of suicide;
- Laboratory test results outside the reference range considered by the investigator to be clinically significant and that would not be consistent with continuation in the study;
- Incorrect enrollment (i.e., the subject does not meet the required inclusion/exclusion criteria) of the subject;
- Development of a condition included in the exclusion criteria may require discontinuation;
- Use of concomitant medication prohibited by the protocol;
- The patient is unable to tolerate the assigned dose of medication;
- Severe non-compliance to protocol as judged by the investigator;
- Patient lost to follow-up;
- The patient becomes pregnant;
- In the case of a neutrophil count of $<1.0x10^9$/L, the test must be repeated within one day. If the second neutrophil count is $<1.0x10^9$/L, this must be reported as an AE and the patient must be discontinued from the study. Additionally, these patients should be monitored with a Complete Blood cell Count (CBC) and White Blood Cell (WBC) differential count weekly until their counts recover. While experiencing neutropenia, patients should avoid invasive procedures such as dental work, rectal exams, or enemas; exposure to people who are obviously ill; and exposure to fresh fruits, vegetables, or flowers. If a patient develops fever or symptoms of infection, he/she should contact his/ or her physician and acquire a CBC count with WBC differential count immediately;
- Patient enters an Inpatient Treatment Program; or,
- The study is terminated by the Investigator, Regulatory Authorities, or the Institutional Review Board of the site.

Patients who discontinue the study will be treated as clinically appropriate as detailed below.

Provision for Follow-Up Care: All subjects who have participated in the evaluation period of this protocol will be provided with psychiatric care (3 visits) at no cost by the investigators for a period of up to 3 months after the end of the study in order to ensure an effective transition to routine clinical care. Patient assistance applications will be completed for those patients requiring financial assistance. Subjects will be provided with appropriate clinical referrals for their follow-up care.

CONCOMITANT MEDICATION:

A benzodiazepine and/or a hypnotic medication are allowed for anxiety or insomnia throughout the study. No other mood stabilizer(s), anticonvulsant, antidepressant, or antipsychotic will be allowed during the study after week 4.

RISKS AND BENEFITS

Once a patient enters the study, he or she will be seen by the study physician (either the principal investigator or a co-investigator) on a weekly to monthly basis. If a patient misses an appointment, he or she will be contacted by study staff to assess safety and reschedule the appointment.

RISKS:

Worsening of symptoms of depression or physical symptoms due to stopping other psychotropic medications may result from study participation, as there is a wash-out period. There is also the risk

that the subject may not respond to the active study medication and worsening of symptoms may result. Suicidal thoughts or a suicide attempt is a serious risk of clinical treatment and hence a serious risk in this study. Seventeen percent of bipolar patients commit suicide.

Serious adverse reactions to lithium include kidney toxicity, hypothyroidism, SIADH (syndrome of inappropriate antidiuretic hormone secretion), and arrhythmias may also occur. Less severe side effects include: acne, diarrhea, polyuria, tremor or weight gain.

Lithium may involve unknown risks to pregnant women, the embryo or fetus, or to infants of nursing women. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient is discontinued from the study.

Finally, there is always the risk of loss of confidentiality. Should there be a breach of confidentiality regarding the patients' diagnosis or treatment, the patient may be exposed to discrimination.

Patients will be required to give a blood sample. The total amount of blood collected during the study will consist of approximately 10 teaspoons of blood, but we anticipate this practice will not be burdensome to patients. When a blood sample is taken, participants may experience temporary discomfort, bruising, and/or infection or blockage of the vein where the needle is put into their arm. On rare occasions, fainting may occur. There are no more than minimal medical or psychological risks associated with this research.

Participants may feel uncomfortable answering some of the questions being asked. If this occurs, the participant will not be forced to answer.

BENEFITS:
There may be no direct benefit to an individual participant. However, lithium is a standard medication for bipolar disorder, and a trial of lithium is standard clinical practice. The outcome of lithium treatment can guide future treatment of a patient. In addition, as most study procedures are clinically indicated as routine, there are several additional potential benefits to participation.
Potential benefits from study participation include an evaluation of symptoms and discussions with the research coordinator, and help in referrals for additional treatment if needed at no cost to the patient. Patients may experience relief from the symptoms of their bipolar. Positive responses to the study medication may provide doctors with other options in the treatment of Bipolar Disorder and therefore benefit other patients. Data collected during this study may help doctors and researchers understand the pathophysiology of bipolar disorder.

FINANCIAL CONSIDERATIONS

Subjects will be compensated $30 for baseline and end of study visits and $15 for each additional visit completed for their time, parking and other travel-related costs.

The study will provide psychiatric evaluations, follow up psychiatric visits for four months, lithium, and laboratory monitoring for those who do not have any insurance or cannot afford the medications. Subjects who have insurance will be responsible for the costs of laboratory monitoring and medications, but will receive psychiatric follow-ups at no cost.

SAFETY

Data Safety & Monitoring Board: Safety monitoring for this study will be conducted by a Data Safety Monitoring Board (DSMB). The chair of this board is Taylor Seagraves, M.D. Dr. Seagraves is not involved as an investigator on any studies with the Mood Disorders Program at UHCMC and is independent. The rest of this committee consists of research staff at the University Hospitals site and includes Stephen Ganocy, PhD - Statistician, Brittany Brownrigg, BA - Data Coordinator and Carla Conroy, MPH - Research Project Manager.

The Chair of the DSMB will conduct real-time monitoring of all Serious Adverse Events that occur. The Principal Investigator will make this determination. This assessment should occur within 24 hours of notification of the Serious Adverse Event. For studies where the Serious Adverse Event is determined to be Study Related, the DSMB Chair will review the Serious Adverse Event within 24 hours and determine whether it is expected or unexpected. The DSMB Chair will ensure that the SAE is reported to the IRB according to established IRB guidelines.

The DSMB meets quarterly, and a review of all study-related Serious Adverse Events will occur with the entire DSMB membership present.

PRIVACY AND CONFIDENTIALITY

Protecting Patient Privacy: Study information is collected in a private office by the research assistants and study doctors. Information will be provided by the participant through interviews and patient rated assessments. In some cases collaborating information may also be obtained from the input of a caregiver, as chosen by the participant, if one is present at the time of the interview. In addition, blood and urine samples will be collected by the laboratories at University Hospitals and the results are returned to the investigators office. Discussions regarding participant information or patient care will be restricted to private offices and involvement will be limited to study related staff.

Certificate of Confidentiality: In order to further protect the patient's privacy, we will apply for a Certificate of Confidentiality (CoC) in order to protect potentially sensitive participant information (i.e. on drug use, etc.). Obtaining the CoC is pending until initial IRB approval of this protocol, which is needed to apply to the NIMH/FDA.

Protecting Data Confidentiality: Patient medical records are stored electronically, in Ambulatory Electronic Medical Record (aEMR), and are password protected. Chart notes and scanned items (i.e. Releases of Information, executed Informed Consent Forms) are entered in to aEMR via restricted means. Therefore, only those who work in the Department of Psychiatry are able to see those notes and scanned items. All subject data will be kept strictly confidential, and no subject-identifying information will be released to anyone outside the project. Confidentiality will be through several mechanisms. Each subject will be assigned an anonymous study unique subject number which will then be used on all study forms, including the electronic data capture system (EDC). Any study forms or paper records that contain subject information will be kept at the clinical sites in secured, locked areas, and coded by unique subject number. Access to all subject data and information, including laboratory specimens, will be restricted to authorized personnel. In the case of computerized data, this restricted access will be assured through user logon IDs and password protection. This protects forms from unauthorized view and modifications as well as inadvertent loss or damage.

FLOW CYTOMETRIC ANALYSIS

Blood Sample

Blood samples will be transferred to CellPrint Biotechnology within 3 hours of the draw. Peripheral blood mononuclear cells will be isolated by ficoll/hypaque discontinuous gradient centrifugation and cryopreserved for subsequent batch analysis. The tubes will be de-identified and the key will remain with the principal investigator. Flow cytometric analysis will be accomplished with the technologists blind to the clinical status of the patient who provided the specimen.

Antibodies

Antibodies to cellular proteins for potential analyses (see Appendix) will be obtained from commercial sources. Each antibody will be tested for use with *CellPrint*™. We anticipate that at least 75% of the proposed antibodies will pass the quality control measures. It is possible that we can replace antibodies that do not pass QC testing with alternate forms or with antibodies targeting molecules not included in the originally proposed panel. The molecules targeted for analyses will cover a wide range of cellular processes potentially affected in bipolar disorder. These cellular processes include apoptosis, cell cycle, cell signaling, macromolecular folding (chaperones), circadian rythym, electron transfer, protein turnover, heat shock response, growth factors, histone modification, inflammation, lipid transport, transcription factors, and ion channels (see appendix).

DATA ANALYSIS PLAN

Statistical Analyses

Primary and secondary analyses: Data monitoring and management will be conducted by the Data Management Unit of the Mood Disorders Program, which is directed by Dr. Stephen Ganocy, PhD.

Primary analysis: The primary analysis will compare differences in molecular expression levels of analytes between patients with bipolar I or II disorder who respond to lithium and those don't respond to. The response is defined as at least 50% improvement from baseline for at least 8 weeks. The results will be analyzed for 2-sided t tests, one-way ANOVA, and Pearson's product moment bivariate correlations.

Secondary analyses: Secondary analyses will compare differences in molecular expression levels of analytes within patient groups and bi- and multi-variate correlation patterns among the analytes assessed. The results will be analyzed for 2-sided t tests, one-way ANOVA, Pearson's product moment bivariate correlations, Fisher's r-to-z transformation to compare correlation coefficients, multiple linear regression, logistic regression, principal component analysis, factor analysis, and cluster analysis.

Appendix – Molecules to be Analyzed

BAG1	Apoptosis
Bax	Apoptosis
cyclin D1	Cell cycle
Glucocorticoid receptor	Cell Signaling
HMGA1a	Cell signaling
mTor	Cell signaling
phospho-mTor	Cell signaling
phospho-Akt(ser473)	Cell signaling
phospho-Akt(thr308)	Cell signaling

phospho-Erk1/2	Cell signaling
phospho-GSK-3b	Cell signaling
phospho-SAPK/JNK	Cell signaling
S100B (glial marker protein)	Cell signaling
Cox-2	Cell Signaling
calmodulin	Cell signaling
DISC1	Cell signaling (also a schizophrenia biomarker)
calnexin	Chaperone
calreticulin	Chaperone
GRP78	Chaperone
Per2	Circadian clock
sepiapterin reductase (SPR)	Electron transfer enzyme
Succinate Dehydrogenase	Electron transfer enzyme
cytochrome C	Electron transfer substrate
Angiotensin-Converting Enzyme (ACE)	Endopeptidase
Calpain 2	Endopeptidase
Matrix Metalloproteinase-3	Endopeptidase
Matrix Metalloproteinase-9, total	Endopeptidase
Brain-derived neurotrophic factor-6 (BDNF-6)	Growth factor
Hepatocyte Growth Factor	Growth factor
HSP70	Heat shock protein
HDAC1	Histone acetylation and deacetylation
C-reactive protein (CRP)	Inflamatory
Carcinoembryonic Antigen (CEA)	Inflamatory
CD40 Ligand (CD154)	Inflamatory
CD5	Inflamatory
EN-RAGE	Inflamatory
IL-1	Inflamatory
Macrophage Inflammatory Protein-1 beta (MIP-1 beta)	Inflamatory
Receptor for advanced glycosylation end products (RAGE)	Inflamatory
Tumor Necrosis Factor - alpha (TNF-a)	Inflamatory
Tumor Necrosis Factor Receptor-Like 2	Inflamatory
Apolipoprotein A1	Lipid transport
Apolipoprotein A2	Lipid transport
Lipoprotein (a)	Lipid transport
FoxP2	Transcription factor
AP-2	Transcription factor
ATF3	Transcription factor
c-fos	Transcription factor
CREB	Transcription factor
NRF2	Transcription factor

Olig1	Transcription factor
phospho-p65	Transcription factor
PU.1	Transcription factor
SP1	Transcription factor
TCF7L2 (TCF4)	Transcription factor
XBP1	Transcription factor
YB-1	Transcription factor
ODZ1 / TENASCIN M - related to ODZ4	Transcription factor (neural)
REST	Transcription factor (neural)
CACNA1C	Voltage dependent ion channel