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IMMEDIATE COMMUNICATION

Discovery and validation of blood biomarkers for suicidality

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Suicides are a leading cause of death in psychiatric patients, and in society at large. Developing more quantitative and objective ways (biomarkers) for predicting and tracking suicidal states would have immediate practical applications and positive societal implications. We undertook such an endeavor. First, building on our previous blood biomarker work in mood disorders and psychosis, we decided to identify blood gene expression biomarkers for suicidality, looking at differential expression of genes in the blood of subjects with a major mood disorder (bipolar disorder), a high-risk population prone to suicidality. We compared no suicidal ideation (SI) states and high SI states using a powerful intrasubject design, as well as an intersubject case–case design, to generate a list of differentially expressed genes. Second, we used a comprehensive Convergent Functional Genomics (CFG) approach to identify and prioritize from the list of differentially expressed gene biomarkers of relevance to suicidality. CFG integrates multiple independent lines of evidence—genetic and functional genomic data—as a Bayesian strategy for identifying and prioritizing findings, reducing the false-positives and false-negatives inherent in each individual approach. Third, we examined whether expression levels of the blood biomarkers identified by us in the live bipolar subject cohort are actually altered in the blood in an age-matched cohort of suicide completers collected from the coroner's office, and report that 13 out of the 41 top CFG scoring biomarkers (32%) show step-wise significant change from no SI to high SI states, and then to the suicide completers group. Six out of them (15%) remained significant after strict Bonferroni correction for multiple comparisons. Fourth, we show that the blood levels of SAT1 (spermidine/spermine N1–acetyltransferase 1), the top biomarker identified by us, at the time of testing for this study, differentiated future as well as past hospitalizations with suicidality, in a live cohort of bipolar disorder subjects, and exhibited a similar but weaker pattern in a live cohort of psychosis (schizophrenia/schizoaffective disorder) subjects. Three other (phosphatase and tensin homolog (PTEN), myristoylated alanine-rich protein kinase C substrate (MARCKS), and mitogen-activated protein kinase kinase kinase 3 (MAP3K3)) of the six biomarkers that survived Bonferroni correction showed similar but weaker effects. Taken together, the prospective and retrospective hospitalization data suggests SAT1, PTEN, MARCKS and MAP3K3 might be not only state biomarkers but trait biomarkers as well. Fifth, we show how a multi-dimensional approach using SAT1 blood expression levels and two simple visual-analog scales for anxiety and mood enhances predictions of future hospitalizations for suicidality in the bipolar cohort (receiver-operating characteristic curve with area under the curve of 0.813). Of note, this simple approach does not directly ask about SI, which some individuals may deny or choose not to share with clinicians. Lastly, we conducted bioinformatic analyses to identify biological pathways, mechanisms and medication targets. Overall, suicidality may be underlined, at least in part, by biological mechanisms related to stress, inflammation and apoptosis.

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INTRODUCTION

'To be, or not to be, that is the question'
W Shakespeare, *Hamlet*

Whatever its evolutionary, teleological and cultural reasons for existing, suicidal behavior is in most cases pathological and leads to irreversible tragedies.[1,2] Paradoxically, given its importance, there are yet no reliable objective tools to assess and track changes in suicidal risk without asking the individuals directly. Such tools are desperately needed, as individuals at risk often choose not to share their ideation or intent with others, for fear of stigma, hospitalization, or that in fact their plans may be thwarted.

A convergence of methods assessing the persons' internal subjective feelings and thoughts, along with external, more objective ratings of actions and behaviors, are used *de facto* in clinical psychiatry. Such an approach is insufficient and is lagging behind those used in other medical specialties. It lacks precision, objectivity and predictive ability.

Our group has previously provided the first proof-of-principle for the use of blood gene expression biomarkers to predict mood state[3] and psychosis symptoms.[4] As the target organ in psychiatry—the brain—cannot be biopsied in live patients, it is

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essential to be able to identify and validate peripheral biomarkers for subsequent practical implementation in clinical settings. We now present a comprehensive and highly reductionist approach for discovering and validating blood biomarkers for suicidality.

We used a Convergent Functional Genomics (CFG) approach to identify and prioritize biomarkers of relevance to suicidality. CFG is a powerful, combined approach for extracting signal from noise in genetic and gene expression studies. The CFG methodology has already been applied to help identify and prioritize candidate genes, pathways and mechanisms for neuropsychiatric disorders, such as bipolar disorder,[5–8] alcoholism,[9] anxiety[10] and schizophrenia,[11] showing reproducibility and predictive ability in independent cohorts.

SUBJECTS AND METHODS

Human subjects

We present data from four cohorts: one live bipolar discovery cohort; one postmortem coroner's office test cohort; and two prospective follow-up live cohorts–one bipolar and one psychosis (schizophrenia/schizoaffective).

These live subjects are part of a larger longitudinal cohort being collected and studied by us. Subjects are recruited from the patient population at the Indianapolis VA Medical Center, the Indiana University School of Medicine, as well as various facilities that serve people with mental illnesses in Indiana. The subjects are recruited largely through referrals from care providers, the use of brochures left in plain sight in public places and mental health clinics, and through word of mouth. Subjects were excluded if they had significant medical or neurological illness or had evidence of active substance abuse or dependence. All subjects understood and signed informed consent forms detailing the research goals, procedure, caveats and safeguards. Subjects completed diagnostic assessments by an extensive structured clinical interview—Diagnostic Interview for Genetic Studies—at a baseline visit, followed by up to three testing visits, 3–6 months apart. At each testing visit, they received a series of psychiatric rating scales, including the Hamilton Rating Scale for Depression-17, which includes a suicidal ideation (SI) rating item (Figure 1), and the blood was drawn. Whole blood (10 ml) was collected in two RNA-stabilizing PAXgene tubes, labeled with an anonymized ID number, and stored at $-80\,^{\circ}C$ in a locked freezer until the time of future processing. Whole-blood (predominantly lymphocyte) RNA was extracted for microarray gene expression studies from the PAXgene tubes, as detailed below. We focused this initial study on a male population because of the demographics of our catchment area (primarily male in a VA Medical Center), and to minimize any potential gender-related effects on gene expression, which would have decreased the discriminative power of our analysis given our relatively small sample size.

Our intrasubject discovery cohort, from which the biomarker data were derived, consisted of nine male Caucasian subjects with bipolar disorder, with multiple visits, who each had a diametric change in SI scores from no SI to high SI from one testing visit to another testing visit. There were 6 subjects with 3 visits each, and 3 subjects with 2 visits each, resulting in a total of 24 blood samples for subsequent microarray studies (Table 1 and Figure 1).

Our postmortem cohort, in which the top biomarker findings were tested, consisted of an age-matched cohort of nine male suicide completers obtained through the Marion County coroner's office (eight Caucasians, one African American) (Table 1 and Supplementary Table S2). We required a last observed alive postmortem interval of 24 h or less, and the cases selected had completed suicide by means other than overdose, which could affect gene expression. Next of kin signed informed consent at the coroner's office for donation of tissues and fluids for research. The samples were collected as part of our INBRAIN initiative (Indiana Center for Biomarker Research in Neuropsychiatry).

The bipolar follow-up cohort ($n=42$) (Table 1) consisted of male Caucasian subjects in whom whole-genome blood gene expression data, including levels of SAT1 (spermidine/spermine N1–acetyltransferase 1), were obtained by us at testing visits over the years as part of our longitudinal study. If the subjects had multiple testing visits, the visit with the highest SAT1 level was selected for this analysis. The subjects' subsequent number of hospitalizations with or without suicidality was tabulated from electronic medical records. The psychosis (schizophrenia/schizoaffective) follow-up cohort ($n=46$) (Supplementary Table S9) similarly consisted of Caucasian subjects in whom whole-genome blood gene expression data, including levels of SAT1, were obtained by us at testing visits over the years as part of our longitudinal study. If the subjects had multiple testing visits, the visit with the highest SAT1 level was selected for this analysis. The subjects' subsequent number of hospitalizations with or without suicidality was tabulated from electronic medical records. A hospitalization was deemed to be without suicidality if suicidality was not listed as a reason for admission, and no SI was described in the admission and discharge medical notes. Conversely, a hospitalization was deemed to be because of suicidality if suicidal acts or intent was listed as a reason for admission, and SI was described in the admission and discharge medical notes.

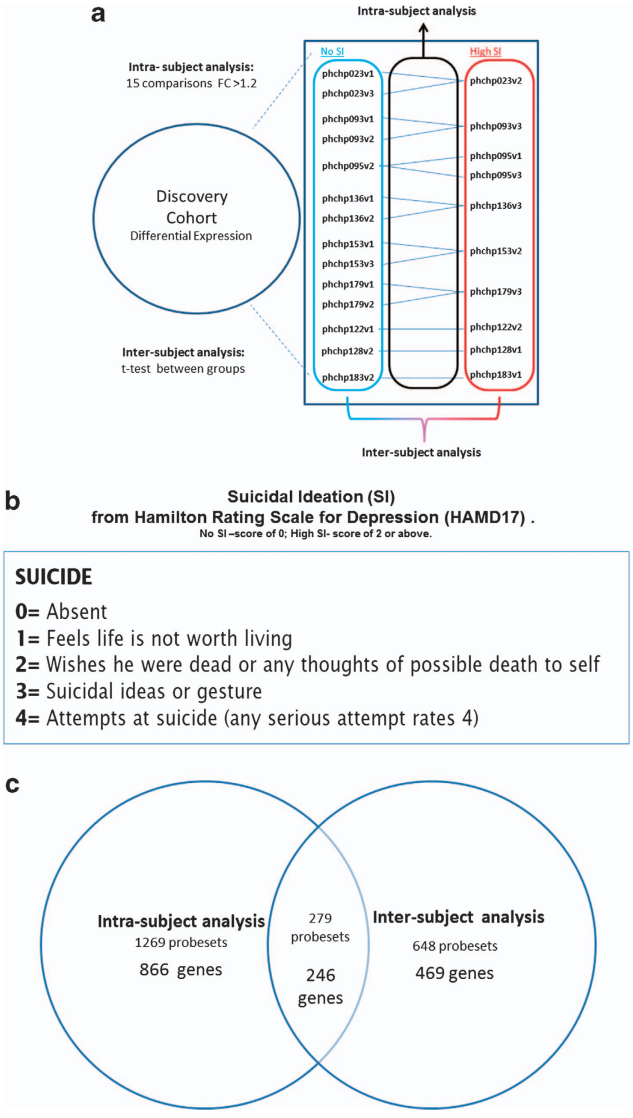


Figure 1. Discovery cohort: intrasubject and intersubject analyses. Phchp### is study ID for each subject. V# after it denotes visit number (1, 2 or 3). (**a**) Design and (**b**) suicidal ideation (SI) scoring. (**c**) Overlapping probesets and genes.

Medications

The subjects in the discovery cohort were all diagnosed with bipolar disorder (Table 1). Their psychiatric medications are listed in Supplementary Table S1. The subjects were on a variety of different psychiatric medications: mood stabilizer, antidepressants, antipsychotics, benzodiazepines and others. Medications can have a strong influence on gene expression. However, our discovery of differentially expressed genes was based on intrasubject analyses, which factor out not only genetic

Table 1. Demographics

A. Individual

Cohort 1: Live bipolar subjects discovery cohort (n = 9) (24 chips)

Subject ID visit	*Diagnosis*	*Age*	*Gender*	*Ethnicity*	*SI*
phchp023v1	Bipolar disorder NOS	52	M	Caucasian	0
phchp023v2	Bipolar disorder NOS	52	M	Caucasian	3
phchp023v3	Bipolar disorder NOS	52	M	Caucasian	0
phchp093v1	Bipolar I disorder	51	M	Caucasian	0
phchp093v2	Bipolar I disorder	51	M	Caucasian	0
phchp093v3	Bipolar I disorder	52	M	Caucasian	3
phchp095v1	Bipolar I disorder	28	M	Caucasian	3
phchp095v2	Bipolar I disorder	29	M	Caucasian	0
phchp095v3	Bipolar I disorder	29	M	Caucasian	2
phchp122v1	Bipolar disorder NOS	51	M	Caucasian	0
phchp122v2	Bipolar disorder NOS	51	M	Caucasian	2
phchp128v1	Bipolar I disorder	45	M	Caucasian	2
phchp128v2	Bipolar I disorder	45	M	Caucasian	0
phchp136v1	Bipolar I disorder	41	M	Caucasian	0
phchp136v2	Bipolar I disorder	41	M	Caucasian	0
phchp136v3	Bipolar I disorder	41	M	Caucasian	3
phchp153v1	Bipolar II disorder	55	M	Caucasian	0
phchp153v2	Bipolar II disorder	55	M	Caucasian	2
phchp153v3	Bipolar II disorder	56	M	Caucasian	0
phchp179v1	Bipolar disorder NOS	36	M	Caucasian	0
phchp179v2	Bipolar disorder NOS	37	M	Caucasian	0
phchp179v3	Bipolar disorder NOS	37	M	Caucasian	3
phchp183v1	Bipolar I disorder	48	M	Caucasian	3
phchp183v2	Bipolar I disorder	48	M	Caucasian	0

Cohort 2: Coroner's office test cohort–suicide completers (n = 9) (9 chips)

Subject ID	*Psychiatric diagnosis*	*Age (years)*	*Gender*	*Ethnicity*	*Suicide by*
INBR009	Bipolar/schizophrenia	59	M	Caucasian	Hanging
INBR011	Depression/ADHD	26	M	Caucasian	GSW to chest
INBR012	Unknown	39	M	Caucasian	GSW to head
INBR013	Depression	68	M	African American	GSW to mouth
INBR014	None	27	M	Caucasian	Hanging
INBR015	None	40	M	Caucasian	Hanging
INBR016	Anxiety/TBI	68	M	Caucasian	GSW to head
INBR017	Depression	56	M	Caucasian	GSW to chest
INBR018	None	65	M	Caucasian	Slit wrist

Cohort 3: Live bipolar subjects prospective follow-up cohort (n = 42)

Subject ID visit	*Diagnosis*	*Age*	*Gender*	*Ethnicity*	*SAT1 levels at testing*	*Years since testing*	*Future hosp. w/o suicidality*	*Future hosp. due to suicidality*	*Frequency of future hosp. w/o suicidality*	*Frequency of future hosp. due to suicidality*
phchp234v1	Bipolar II disorder	44	M	Caucasian	1955.20	0.83	0	0	0.00	0.00
phchp053v2	Bipolar I disorder	58	M	Caucasian	2178.30	5.67	4	0	0.71	0.00
phchp152v1	Bipolar I disorder	45	M	Caucasian	2178.80	2.33	0	0	0.00	0.00
phchp122v1	Bipolar disorder NOS	51	M	Caucasian	2245.60	0.58	0	0	0.00	0.00
phchp190v3	Bipolar disorder NOS	50	M	Caucasian	2300.60	1.25	0	0	0.00	0.00
phchp020v3	Bipolar disorder NOS	63	M	Caucasian	2342.60	4.08	0	0	0.00	0.00
phchp113v1	Bipolar I disorder	37	M	Caucasian	2437.40	3.00	0	0	0.00	0.00
phchp132v2	Bipolar I disorder	51	M	Caucasian	2558.90	2.33	0	0	0.00	0.00
phchp184v3	Bipolar disorder NOS	64	M	Caucasian	2575.40	1.33	0	0	0.00	0.00
phchp039v3	Bipolar I disorder	52	M	Caucasian	2580.10	5.75	0	0	0.00	0.00
phchp147v1	Bipolar II disorder	38	M	Caucasian	2582.80	2.25	0	0	0.00	0.00
phchp178v1	Bipolar I disorder	49	M	Caucasian	2616.80	1.00	0	0	0.00	0.00
phchp136v3	Bipolar I disorder	41	M	Caucasian	2635.90	2.00	0	0	0.00	0.00
phchp045v3	Bipolar I disorder	36	M	Caucasian	2721.00	5.42	0	0	0.00	0.00
phchp224v1	Bipolar I disorder	59	M	Caucasian	2748.10	1.08	1	1	0.92	0.92
phchp183v1	Bipolar I disorder	48	M	Caucasian	2750.90	0.42	2	1	4.80	2.40
phchp171v2	Bipolar disorder NOS	36	M	Caucasian	2795.70	1.50	0	0	0.00	0.00
phchp166v1	Bipolar disorder NOS	56	M	Caucasian	2829.60	1.92	0	0	0.00	0.00
phchp253v1	Bipolar disorder NOS	25	M	Caucasian	2888.50	1.00	0	0	0.00	0.00
phchp186v1	Bipolar II disorder	43	M	Caucasian	2901.50	1.67	0	0	0.00	0.00
phchp079v2	Bipolar disorder	44	M	Caucasian	3053.20	4.50	0	0	0.00	0.00
phchp128v1	Bipolar I Disorder	45	M	Caucasian	3118.60	2.67	0	0	0.00	0.00
phchp080v1	Bipolar I disorder	44	M	Caucasian	3153.60	5.00	0	0	0.00	0.00
phchp088v1	Bipolar I disorder	44	M	Caucasian	3194.10	4.58	0	10	0.00	2.18
phchp109v1	Bipolar I disorder	22	M	Caucasian	3200.80	3.00	1	2	0.33	0.67

Table 1. (Continued)

Cohort 3: Live bipolar subjects prospective follow-up cohort (n = *42*)

Subject ID visit	*Diagnosis*	*Age*	*Gender*	*Ethnicity*	*SAT1 levels at testing*	*Years since testing*	*Future hosp. w/o suicidality*	*Future hosp. due to suicidality*	*Frequency of future hosp. w/o suicidality*	*Frequency of future hosp. due to suicidality*
phchp134v3	Bipolar II disorder	59	M	Caucasian	3202.30	1.92	0	0	0.00	0.00
phchp153v1	Bipolar II disorder	55	M	Caucasian	3304.90	2.00	0	0	0.00	0.00
phchp274v2	Bipolar disorder NOS	48	M	Caucasian	3349.00	0.50	0	0	0.00	0.00
phchp140v3	Bipolar II disorder	38	M	Caucasian	3393.80	1.92	0	0	0.00	0.00
phchp030v3	Bipolar I disorder	49	M	Caucasian	3395.20	5.92	0	3	0.00	0.51
phchp124v1	Bipolar I disorder	53	M	Caucasian	3660.90	2.50	0	6	0.00	2.40
phchp095v3	Bipolar I disorder	29	M	Caucasian	3695.40	0.33	0	1	0.00	3.00
phchp100v1	Bipolar I Disorder	28	M	Caucasian	3767.80	1.58	0	0	0.00	0.00
phchp210v3	Bipolar I disorder	44	M	Caucasian	3844.60	0.50	0	0	0.00	0.00
phchp219v1	Bipolar disorder NOS	61	M	Caucasian	3845.10	1.17	0	0	0.00	0.00
phchp031v3	Bipolar I disorder	52	M	Caucasian	4080.70	4.08	1	0	0.24	0.00
phchp093v3	Bipolar I disorder	52	M	Caucasian	4137.40	2.67	0	1	0.00	0.38
phchp067v1	Bipolar II disorder	39	M	Caucasian	4214.70	5.58	0	0	0.00	0.00
phchp142v3	Bipolar I disorder	55	M	Caucasian	4310.70	1.92	0	0	0.00	0.00
phchp112v2	Bipolar I disorder	46	M	Caucasian	4410.40	1.33	0	0	0.00	0.00
phchp149v2	Bipolar disorder NOS	45	M	Caucasian	4586.90	2.00	1	0	0.50	0.00
phchp117v1	Bipolar I disorder	43	M	Caucasian	6531.10	3.00	0	0	0.00	0.00

B. Aggregate

SI score	*No SI (0)*	*High SI (2–4)*	*Overall*
Live bipolar subjects discovery cohort (n = *9*)			
Number of subjects (number of chips)	9 (14)	9 (10)	9 (24)
Age (years)			
Mean	46.1	43.8	45.1
s.d.	8.1	9.7	8.7
Range	29–56	28–55	28–56
Ethnicity (Caucasian/African American)	(9/0)	(9/0)	(9/0)
Coroner's office test cohort–suicide completers (n = *9*)			
Number of subjects (number of chips)	9 (9)		
Age (years)			
Mean	49.8		
s.d.	17		
Range	26–68		
Live bipolar subjects prospective follow-up cohort (n = *42*)			
SAT1 Levels	*Lower tertile*	*Upper tertile*	*Overall*
Number of subjects	14	14	42
Age			
mean	48.5	45.3	46.2
(s.d.)	9	9.5	9.9
range	36–64	28–61	22–64
Ethnicity (Caucasian/African-American)	(14/0)	(14/0)	(42/0)

Abbreviations: M, male; NOS, not otherwise specified; ADHD, attention-deficit hyperactivity disorder; TBI, traumatic brain injury; hosp. hospitalization; GSW, gunshot wound.; SI, suicidal ideation; SAT1, spermidine/spermine N1–acetyltransferase 1.
Diagnosis established by comprehensive structured clinical interview. SI question is from the Hamilton Rating Scale for Depression obtained at the time of blood draw for each subject.

background effects but also medication effects, as the subjects had no major medication changes between visits. Moreover, there was no consistent pattern in any particular type of medication, or between any change in medications and SI, in the rare instances where there were changes in medications between visits.

Human blood gene expression experiments and analyses

RNA extraction. Whole blood (2.5–5 ml) was collected into each PaxGene tube by routine venipuncture. PaxGene tubes contain proprietary reagents for the stabilization of RNA. The cells from whole blood were concentrated by centrifugation, the pellet washed, resuspended and incubated in buffers containing Proteinase K for protein digestion. A second centrifugation step was done to remove residual cell debris. After the addition of ethanol for an optimal binding condition, the lysate was applied to a silica-gel membrane/column. The RNA bound to the membrane as the column was centrifuged, and contaminants were removed in three wash steps. The RNA was then eluted using diethylpyrocarbonate-treated water. The protocol for RNA extraction is carried out on a QIAgen QIAcube.

Sample labeling. Sample labeling was performed using the Ambion MessageAmp II-Biotin*Enhanced* antisense RNA (aRNA) amplification kit. The procedure is briefly outlined below and involves the following steps:

1. Reverse transcription to synthesize first-strand cDNA was primed with the T7 oligo(dT) primer to synthesize cDNA containing a T7 promoter sequence.
2. Second-strand cDNA synthesis converted the single-stranded cDNA into a double-stranded DNA template for transcription. The reaction employed DNA polymerase and RNase H to simultaneously degrade the RNA and synthesize the second-strand cDNA.
3. cDNA purification removed RNA, primers, enzymes and salts that would have inhibited *in vitro* transcription.
4. *In vitro* transcription to synthesize aRNA with biotin–NTP Mix generated multiple copies of biotin-modified aRNA from the double-stranded cDNA templates; this is the amplification step.
5. aRNA purification removed unincorporated NTPs, salts, enzymes and inorganic phosphate to improve the stability of the biotin-modified aRNA.
6. aRNA fragmentation: the amplified RNA is fragmented in a reaction that employs a metal-induced hydrolysis to fragment the aRNA. The fragmented labeled aRNA is now ready for hybridization to the Affymetrix microarray chip (Affymetrix, Santa Clara, CA, USA).

Microarrays. Biotin-labeled aRNAs were hybridized to Affymetrix HG-U133 Plus 2.0 GeneChips (Affymetrix; with over 40 000 genes and expressed sequence tags), according to the manufacturer's protocols http://www.affymetrix.com/support/technical/manual/expression_manual.affx. Arrays were stained using standard Affymetrix protocols for antibody signal amplification and scanned on an Affymetrix GeneArray 2500 scanner with a target intensity set at 250. Quality-control measures, including 30/50 ratios for glyceraldehyde 3-phosphate dehydrogenase and β-actin, scale factors, background and *Q*–values, were within acceptable limits.

Analysis. We have used the subject's SI scores at the time of blood collection (0—no SI compared with 2 and above—high SI). We looked at gene expression differences between the no SI and the high SI visits, using both an intrasubject and an intersubject design (Figure 1).

Differential gene expression analyses in the discovery cohort

We imported all Affymetrix microarray data as cel files into Partek Genomic Suites 6.6 software package (Partek Incorporated, St Louis, MI, USA). Using only the perfect match values, we ran a robust multi-array analysis (RMA), background corrected with quantile normalization and a median polish probeset summarization of all 24 chips, to obtain the normalized expression levels of all probesets for each chip. Then, to establish a list of differentially expressed probesets we ran two analyses.

An intrasubject analysis using a fold change in expression of at least 1.2 between high- and no SI visits within each subject was performed. There were in total 15 comparisons. Probesets that had a 1.2-fold change were then assigned either a 1 (increased in high SI) or a -1 (decreased in high SI) in each comparison. These values were then summed for each probeset across the 15 comparisons, yielding a range of scores between -11 and 12. The probesets in the top 5% (1269 probesets, $<5\%$ of 54 675 total probesets) had an absolute (without sign) score value of 7 and greater, and received an internal CFG score of 1 point. The probesets in the top 0.1% (24 probesets, $<0.1\%$ of 54 675 total probesets) had an absolute score of 11 and greater, and received an internal CFG score of 3 points.

In addition, an intersubject analysis using *t*-test (two-tailed, unequal variance) was performed to find probesets differentially expressed between high SI and no SI chips (Figure 1), resulting in 648 probesets with $P<0.05$. Probesets with a $P<0.05$ received an internal CFG score of 1 point, whereas probesets with $P<0.001$ received 3 points.

We further filtered results by only selecting probesets that overlapped between the intrasubject and the intersubject analyses, resulting in 279 probesets corresponding to 246 unique genes. Gene names for the probesets were identified using Partek and NetAffyx (Affymetrix) for Affymetrix HG-U133 Plus 2.0 GeneChips, followed by GeneCards to confirm the primary gene symbol. In addition, for those probesets that were not assigned a gene name by Partek or NetAffyx, we used the UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) to directly map them to known genes. Genes were then scored using our manually curated CFG databases as described below (Figure 2).

Convergent Functional Genomics

Databases. We have established in our laboratory (Laboratory of Neurophenomics, Indiana University School of Medicine, www.neurophenomics.info) manually curated databases of all the human gene expression (postmortem brain, blood and cell cultures), human genetics (association, copy number variations and linkage), and animal model gene expression and genetic studies published to date on psychiatric disorders.[12] Only the findings deemed significant in the primary publication, by the study authors, using their particular experimental design and thresholds, are included in our databases. Our databases include only primary literature data and do not include review papers or other secondary data integration analyses to avoid redundancy and circularity. These large and constantly updated databases have been used in our CFG cross validation and prioritization (Figure 2).

Human postmortem brain gene expression evidence. Information about genes was obtained and imported in our databases by searching the primary literature with PubMed (http://ncbi.nlm.nih.gov/PubMed), using various combinations of keywords (gene name, suicide, suicide gene expression and human brain). Postmortem convergence was deemed to occur for a gene if there were published reports of human postmortem data showing changes in expression of that gene in brains from patients who died from suicide.

Human blood and other peripheral tissue gene expression data. For human blood gene expression, evidence was extracted from our database compiled by a similar method as above, performing a search of the primary literature by entering various combinations of keywords (gene name, suicide, suicide gene expression, lymphoblasts and blood). No matches were found for our final list of differentially expressed genes.

Human genetic evidence (association and linkage). To designate convergence for a particular gene, the gene had to have independent published evidence of association or linkage for suicide. For linkage, the location of each gene was obtained through GeneCards (http://www.genecards.org), and the sex averaged cM location of the start of the gene was then obtained through http://compgen.rutgers.edu/mapinterpolator. For linkage convergence, the start of the gene had to map within 5 cM of the location of a marker linked to the disorder.

CFG scoring. For CFG analysis (Figure 2), two external cross-validating lines of evidence were weighted such that findings in human postmortem brain tissue, the target organ, were prioritized over genetic findings, by giving it twice as many points. Human brain expression evidence was given 4 points, whereas human genetic evidence was given a maximum of 2 points for association and 1 point for linkage. Each line of evidence was capped in such a way that any positive findings within that line of evidence result in maximum points, regardless of how many different studies support that single line of evidence, to avoid potential popularity biases.

In addition to our external score, we also prioritized genes based upon the initial differential expression analyses used to identify them. Probesets identified by differential expression analyses could receive a maximum of 6 points (1 or 3 points from intrasubject analyses, and 1 or 3 points from intersubject analyses).

Thus, the maximum possible total CFG score for each gene was 12 points (6 points for the internal score + 6 points for the external score), with the internal and external evidence weighted equally. The scoring system was decided upon before the analysis. It has not escaped our attention that other ways of scoring the lines of evidence may give slightly different results in terms of prioritization, if not in terms of the list of genes *per se*. Nevertheless, we feel this simple scoring system provides a good separation of genes based on differential expression and on independent cross-validating evidence in the field (Figure 2).

Pathway analyses

IPA 9.0 (Ingenuity Systems, www.ingenuity.com, Redwood City, CA, USA) was used to analyze the biological roles, including top canonical pathways and diseases, of the candidate genes resulting from our work (Table 3 and Supplementary Table S4), as well as to identify genes in our data sets that

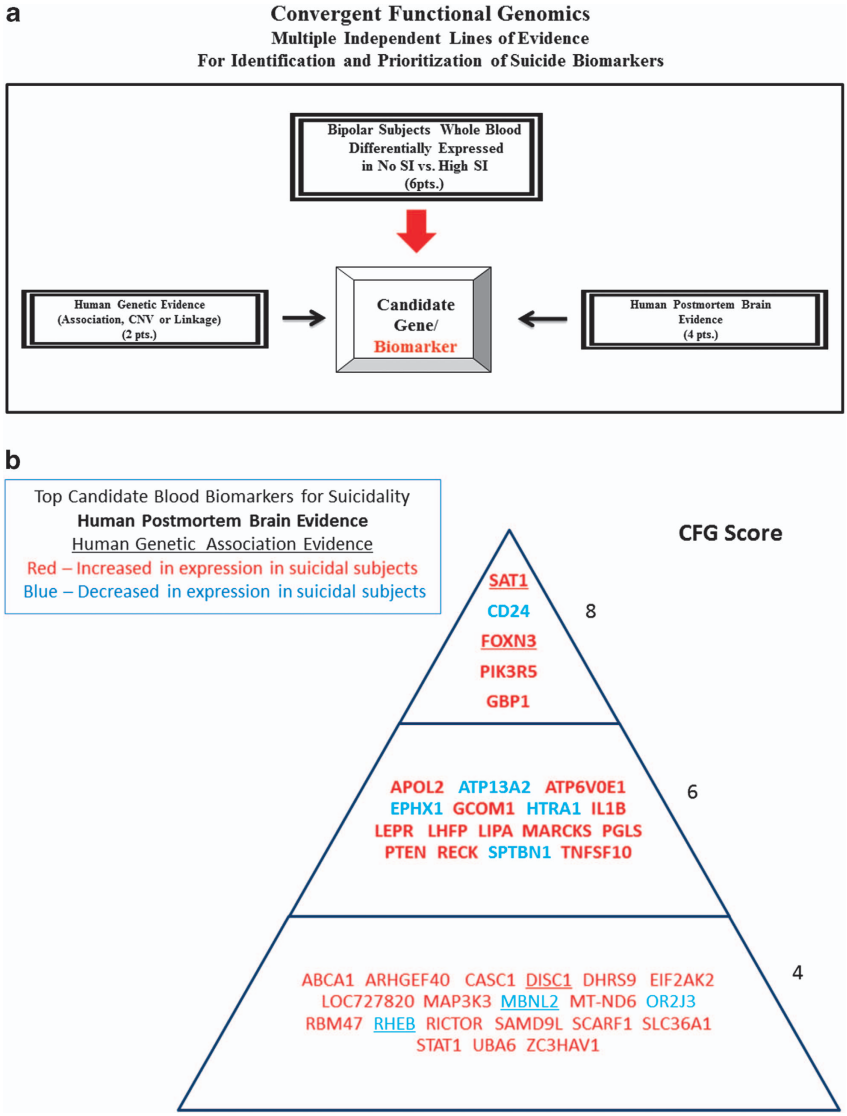


Figure 2. Convergent Functional Genomics approach for identification and prioritization of genomic biomarkers for suicidality.

are the target of existing drugs (Supplementary Table S5). Pathways were identified from the IPA library of canonical pathways that were most significantly associated with genes in our data set. The significance of the association between the data set and the canonical pathway was measured in two ways: (1) A ratio of the number of molecules from the data set that map to the pathway divided by the total number of molecules that map to the canonical pathway is displayed. (2) Fisher's exact test was used to calculate a *P*-value determining the probability that the association between the genes in the data set and the canonical pathway is explained by chance alone. We also conducted a Kyoto Encyclopedia of Genes and Genomes pathway analysis through the Partek Genomic Suites 6.6 software package.

Validation analyses

We imported the nine Affymetrix microarray data files from the suicide completers cohort as cel files into the Partek Genomic Suites 6.6 software package (Partek Incorporated). We then ran a RMA, background corrected with quantile normalization, and a median polish probeset summarization of all the chips from the discovery and validation cohort ($24+9=33$ chips), to obtain the normalized expression levels of all probesets for each chip. Partek normalizes expression data into a log base of 2 for visualization purposes. We non-log-transformed expression data by taking 2 to the power of the transformed expression value. We then used the non-log-transformed expression data to compare expression levels of biomarkers in the different groups (Figure 3). One-tail Student's *t*-tests with unequal variance, one-way ANOVA and Bonferonni corrections were used for statistical comparisons.

For live cohorts' future hospitalization analyses in bipolar disorder and schizophrenia/schizoaffective, we similarly RMA normalized each cohort, before looking at biomarker levels in individual subjects. One-tail Student's *t*-tests with equal variance were used for statistical comparisons. Receiver-operating characteristic curves were calculated using SPSS software for each of the four-dimensional analyses, predicting the state variable of hospitalizations due to suicidality.

RESULTS

Discovery

We conducted whole-genome gene expression profiling in the blood samples from a longitudinally followed homogeneous cohort of male subjects with a major mood disorder (bipolar disorder) that predisposes to suicidality. One in three individuals with bipolar disorder attempt suicide during their lifetime.[13] The samples were collected at repeated visits, 3–6 months apart. State information about SI was collected from a questionnaire

Table 2. Top gene expression biomarkers for suicidality

Gene symbol/gene name	*Probesets*	*Change*	*Differential expression score*	*Prior human genetic evidence*	*Prior human brain expression evidence*	*Total CFG score*
SAT1 Spermidine/spermine N1–acetyltransferase 1	203455_s_at	I	2	(Association) Suicide attempt;[45] suicide[46]	Suicide in depression (D) PFC[47] Suicide (D) AMY, PFC, HIP, THAL[39] Suicide (D) PFC[48] Suicide (D) PFC[49] Suicide (D) PFC[50] Suicide (D) PFC[51] Suicide (D) PFC[52] Suicide (D) PFC[46]	8
CD24 CD24 molecule	209772_s_at	D	4		Suicide in mood disorders (D) NAC[15]	8
FOXN3 Forkhead box N3	230790_x_at	I	2	(Association) Suicide[53]	Suicide (I) PFC[53]	8
GBP1 Guanylate binding protein 1, interferon-inducible, 67 kDa	231577_s_at 202269_x_at 202270_at	I	4 2 2		Suicide in mood disorders (D) NAC[15]	8 6 6
PIK3R5 Phosphoinositide-3-kinase, regulatory subunit 5	227553_at	I	4		Suicide in mood disorders (D) PFC[15]	8
APOL2 Apolipoprotein L2	221653_x_at	I	2		Suicide PFC (I)[54]	6
ATP13A2 ATPase type 13A2	218608_at	D	2		Suicide (D)[15]	6
ATP6V0E1 ATPase, H+ transporting, lysosomal 9 kDa, V0 subunit e1	214149_s_at 214244_s_at	I	2		Suicide (D) PFC[46]	6
EPHX1 Epoxide hydrolase 1, microsomal (xenobiotic)	202017_at	D	2		Suicide in schizophrenia (D) PFC[55]	6
GCOM1 GRINL1A complex locus 1	239099_at	I	2		Suicide in depression (D) PFC[56]	6
HTRA1 HtrA serine peptidase 1	201185_at	D	2		Suicide (I)[15]	6
IL1B Interleukin 1, beta	39402_at	I	2		Suicide (I) PFC[57]	6
LEPR Leptin receptor	211354_s_at	D	2		Suicide (D) PFC[56] (D) PFC[58] (D) HIP[59] Suicide in depression (I) PFC[60]	6
LHFP Lipoma HMGIC fusion partner	218656_s_at	I	2		Suicide in mood disorders (I) NAC[15]	6
LIPA Lipase A	236156_at	I	2		Violent suicide (I) PFC[61]	6
MARCKS Myristoylated alanine-rich protein kinase C substrate	213002_at	I	2		Suicide in depression (I)[62]	6
PGLS 6-Phosphogluconolactonase	230699_at	I	2		Suicide PFC (D)[54]	6
PTEN Phosphatase and tensin homolog	222176_at	I	2		Suicide PFC, HIP (I)[26]	6
RECK Reversion-inducing-cysteine-rich protein with kazal motifs	216153_x_at	I	2		Suicide (I) PFC[15]	6
SPTBN1 Spectrin, beta, non-erythrocytic 1	200671_s_at	D	2		Suicide in mood disorders (I) NAC[15]	6
TNFSF10 Tumor necrosis factor (ligand) superfamily, member 10	202688_at 202687_s_at 214329_x_at	I	2		Suicide in schizophrenia (I) PFC[55] Suicide in depression (I) PFC[60]	6
ABCA1 ATP-binding cassette, subfamily A (ABC1), member 1	203504_s_at	I	4			4
ARHGEF40 (FLJ10357) Rho guanine nucleotide exchange factor (GEF) 40	241631_at	I	4			4
CASC1 Cancer susceptibility candidate 1	220168_at	I	4			4
DHRS9 Dehydrogenase/reductase (SDR family) member 9	219799_s_at	I	4			4

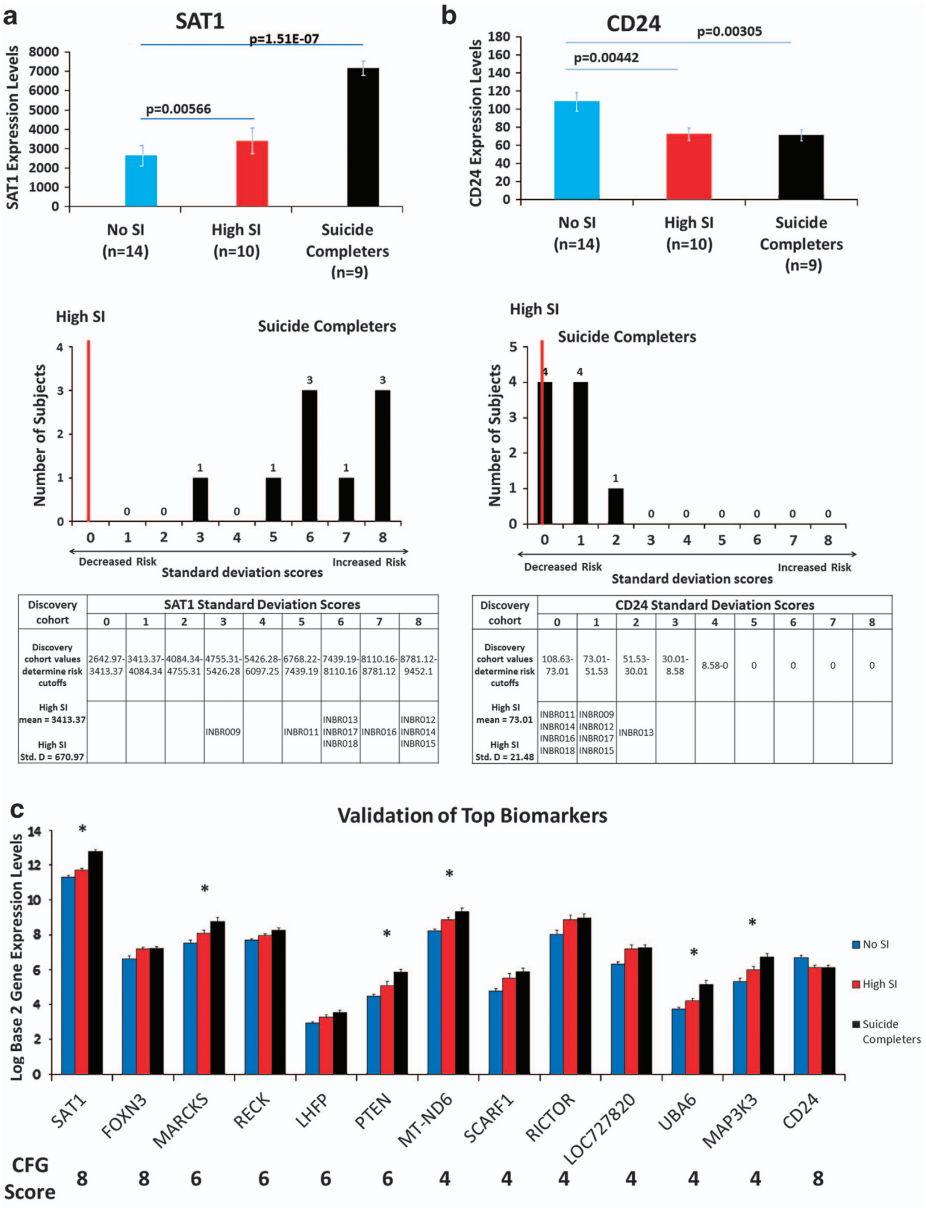
Table 2. (Continued)

Gene symbol/gene name	*Probesets*	*Change*	*Differential expression score*	*Prior human genetic evidence*	*Prior human brain expression evidence*	*Total CFG score*
DISC1 Disrupted in schizophrenia 1	244642_at	I	2	(Association) Suicide[53]		4
EIF2AK2 Eukaryotic translation initiation factor 2-alpha kinase 2	204211_x_at	I	4			4
LOC727820 Uncharacterized LOC727820	231247_s_at	I	4			4
MAP3K3 Mitogen-activated protein kinase kinase kinase 3	242117_at	I	4			4
MBNL2 Muscleblind-like 2 (Drosophila)	205017_s_at	D	2	(Association) Suicide[53]		4
MT-ND6 (ND6) Mitochondrially encoded NADH dehydrogenase 6	1553575_at	I	4			4
OR2J3 Olfactory receptor, family 2, subfamily J, member 3	217334_at	D	4			4
RBM47 RNA binding motif protein 47	1565597_at	I	4			4
RHEB Ras homolog enriched in brain	227633_at	D	2	(Association) Suicide[63]		4
RICTOR RPTOR independent companion of MTOR, complex 2	228248_at	I	4			4
SAMD9L Sterile alpha motif domain containing 9-like	243271_at; 230036_at	I	4			4
SCARF1 Scavenger receptor class F, member 1	206995_x_at	I	4			4
SLC36A1 Solute carrier family 36 (proton/amino acid symporter), member 1	213119_at	I	4			4
STAT1 Signal transducer and activator of transcription 1, 91kDa	232375_at	I	4			4
UBA6 Ubiquitin-like modifier activating enzyme 6	236879_at	I	4			4
ZC3HAV1 Zinc finger CCCH-type, antiviral 1	1563075_s_at	I	4			4
COX5B Cytochrome *c* oxidase subunit Vb	213736_at	I	2	(Linkage) 2q11.2[64]		3
SMARCA1 SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 1	203874_s_at	I	2	(Linkage) Xq25[50]		3
DBP D-box binding protein	209782_s_at	D	2			2

Abbreviations: I, increased in expression; D, decreased in expression; AMY, amygdala; PFC, prefrontal cortex; THAL, thalamus; HIP, hippocampus; NAC, nucleus accumbens.
The underlined gene names have human genetic association evidence.

Figure 3. Testing of biomarkers in suicide completers. (**a**) Upper: SAT1 (spermidine/spermine N1–acetyltransferase 1) expression is significantly increased ($P = 0.0057$) in our discovery work between subjects with high suicidal ideation (SI) (mean = 3413.37) and those reporting no SI (mean = 2642.97). Our test cohort of suicide completers (mean = 7171.51) showed significantly greater expression of SAT1 than both high SI ($P = 7.27e\text{-}07$) and no SI ($P = 1.51e\text{-}07$) groups from the discovery cohort. Lower: a suicide risk score was calculated by scoring the s.d. band a subject fell within as derived from the high SI discovery cohort, starting from the mean of the high-SI discovery cohort. A score of 0 indicates the subject falling between the means of the high SI and no SI subjects in the discovery cohort. A score of 1 means between the mean of the high SI and the first s.d. above it, score of 2 between the first and second s.d., score of 3 between the second and third s.d., and so on. Red line marks where the average SAT1 gene expression in high SI subjects would fall. (**b**) Upper: CD24 (CD24 molecule/small cell lung carcinoma cluster 4 antigen) expression was significantly decreased ($P = 0.0044$) within the discovery cohort between subjects reporting high SI (mean = 73.01) and no SI (mean = 108.634). The test cohort of suicide completers (mean = 71.61) was also significantly decreased ($P = 0.0031$) when compared with subjects reporting no SI. Lower: suicide risk score defined as the s.d. band in which the subject expression fell below the mean of the high-SI discovery cohort. Red line marks where the average *CD24* gene expression in high SI subjects would fall. (**c**) Testing of top candidate biomarkers for suicidality. Thirteen out of the 41 CFG top-scoring biomarkers from Figure 2b (32%) showed step-wise significant change from no SI to high SI, to the validation suicide completers group. Six out of them (15%) remained significant after strict Bonferroni correction for multiple comparisons. The top CFG scoring biomarker SAT1 remained the top biomarker after validation.

administered at the time of each blood draw (Table 1). Out of 75 bipolar subjects (with a total of 174 visits) followed longitudinally in our study, there were 9 subjects that switched from a no SI (SI score of 0) to a high SI state (SI score of 2 and above) at different visits, which was our intended study group. We used a powerful intrasubject design to analyze data from these 9 subjects and their



Discovery cohort	SAT1 Standard Deviation Scores								
	0	1	2	3	4	5	6	7	8
Discovery cohort values determine risk cutoffs	2642.97-3413.37	3413.37-4084.34	4084.34-4755.31	4755.31-5426.28	5426.28-6097.25	6768.22-7439.19	7439.19-8110.16	8110.16-8781.12	8781.12-9452.1
High SI mean = 3413.37				INBR009		INBR011	INBR013 INBR017 INBR018	INBR016	INBR012 INBR014 INBR015
High SI Std. D = 670.97									

Discovery cohort	CD24 Standard Deviation Scores								
	0	1	2	3	4	5	6	7	8
Discovery cohort values determine risk cutoffs	108.63-73.01	73.01-51.53	51.53-30.01	30.01-8.58	8.58-0	0	0	0	0
High SI mean = 73.01	INBR011 INBR014 INBR016 INBR018	INBR009 INBR012 INBR017 INBR015	INBR013						
High SI Std. D = 21.48									

CFG Score	Gene	Direction of Change	P-Value (One-Way ANOVA)
8	**SAT1**	**I**	**2.91E-13**
4	**UBA6**	**I**	**8.94E-05**
6	**MARCKS**	**I**	**0.000187221**
6	**PTEN**	**I**	**0.000298958**
4	**MT-ND6**	**I**	**0.000391061**
4	**MAP3K3**	**I**	**0.000777774**
6	LHFP	I	0.001535921
4	LOC727820	I	0.003706529
8	CD24	D	0.006082658
6	RECK	I	0.009035235
8	FOXN3	I	0.010040264
4	SCARF1	I	0.014880001
4	RICTOR	I	0.040726456

Table 3. Underlying biology

A. Pathways

	INGENUITY pathways			*KEGG pathways*		
No.	*Top canonical pathways*	*P-value*	*Ratio*	*Pathway name*	*Enrichment score*	*Enrichment P-value*
CFG score ⩾ 6.0; N = *21 genes*						
1	Role of tissue factor in cancer	2.63E − 04	3/115 (0.026)	**Apoptosis**	6.69102	0.001242
2	Dendritic cell maturation	9.83E − 04	3/207 (0.014)	Measles	6.06369	0.002326
3	Melanoma signaling	1.13E − 03	2/46 (0.043)	Endometrial cancer	4.96787	0.006958
4	**DHA signaling**	1.18E − 03	2/49 (0.041)	Influenza A	4.90223	0.00743
5	Endometrial cancer signaling	1.69E − 03	2/57 (0.035)	Phosphatidylinositol signaling system	4.85448	0.007793
CFG score ⩾ 4.0; N = *41 genes*						
1	NF-κB signaling	4.42E − 04	4/175 (0.023)	Measles	8.7667	0.000156
2	Dendritic cell maturation	5.38E − 04	4/207 (0.019)	Influenza A	6.87308	0.001035
3	PDGF signaling	7.5E − 04	3/85 (0.035)	mTOR signaling pathway	6.34986	0.001747
4	Role of pattern recognition receptors in recognition of bacteria and viruses	1.14E − 03	3/106 (0.028)	**Apoptosis**	4.75687	0.008592
5	Role of tissue factor in cancer	1.78E − 03	3/115 (0.026)	Toll-like receptor signaling pathway	4.37269	0.012617

B. Disease and disorders

INGENUITY

No.	*Diseases and disorders*	*P-value*	*Number of molecules*
CFG score ⩾ 6.0; N = *21 genes*			
1	**Cancer**	1.22E − 06 to 4.54E − 03	14
2	Connective tissue disorders	2.19E − 04 to 3.41E − 03	8
3	**Inflammatory disease**	2.19E − 04 to 4.54E − 03	8
4	Skeletal and muscular disorders	2.19E − 04 to 4.42E − 03	9
5	Gastrointestinal disease	2.22E − 04 to 4.54E − 03	12
CFG score ⩾ 4.0; N = *41 genes*			
1	**Cancer**	4.51E − 06 to 6.45E − 03	20
2	**Inflammatory response**	2.70E − 05 to 6.45E − 03	12
3	Antimicrobial response	9.95E − 05 to 6.45E − 03	4
4	Infectious disease	1.25E − 04 to 5.52E − 03	6
5	Connective tissue disorders	1.53E − 04 to 6.45E − 03	11

Abbreviations: KEGG, Kyoto Encyclopedia of Genes and Genomes; CFG, Convergent Functional Genomics; DHA, docosahexaenoic acid; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB.

24 visits. An intrasubject design factors out genetic variability, as well as some medications, lifestyle and demographic effects on gene expression, permitting identification of relevant signal with Ns as small as 1.[14] An ancillary benefit of an intrasubject design may be accuracy/consistency of self-report of psychiatric symptoms ('phene expression'), similar in rationale to the signal-detection benefits it provides in gene expression. We also used an overall intersubject case–case analysis, to identify genes differentially expressed in the blood in no SI states versus high SI states (Figure 1). The number of subjects that met our criteria and were analyzed is small, but comparable to those in human postmortem brain gene expression studies of suicide.[15] We are indeed treating the blood samples as surrogate tissue for brains, with the caveat that they are not the real target organ. However, with the blood samples from live human subjects we have the advantages of *in-vivo* accessibility, better knowledge of the mental state at the time of collection, less technical artifacts and especially of being able to do powerful intrasubject analyses from visit to visit. We considered and differentially scored only the very top 0.1 and 5% of the gene expression probesets distributions, and also required overlap between the intrasubject and intersubject analyses of gene expression changes. Such a restrictive approach was used as a way of minimizing false positives, even at the risk of having false negatives (Figure 1c). For example, there were genes on each of the two lists, from intra- and intersubject analyses, that had clear prior evidence for involvement in suicidality, such as MT1E[15] and GSK3B, respectively,[16] but were not included in our subsequent analyses because they were not in the overlap.

We then used a CFG approach (Figure 2) to cross match the list of 246 overlapping top differentially expressed genes from the blood samples with other key lines of evidence (human postmortem brain data and human genetic data) implicating them in suicidality, as a way of identifying and prioritizing disease-relevant genomic biomarkers, extracting generalizable signal out of potential cohort-specific residual noise and genetic heterogeneity. We have built in our lab manually curated databases of the psychiatric genomic and proteomic literature to date, for use in CFG analyses.[12,17–19] The CFG approach is thus a *de facto* field-wide collaboration. We use in essence, in a Bayesian fashion, the whole body of knowledge in the field to leverage findings from

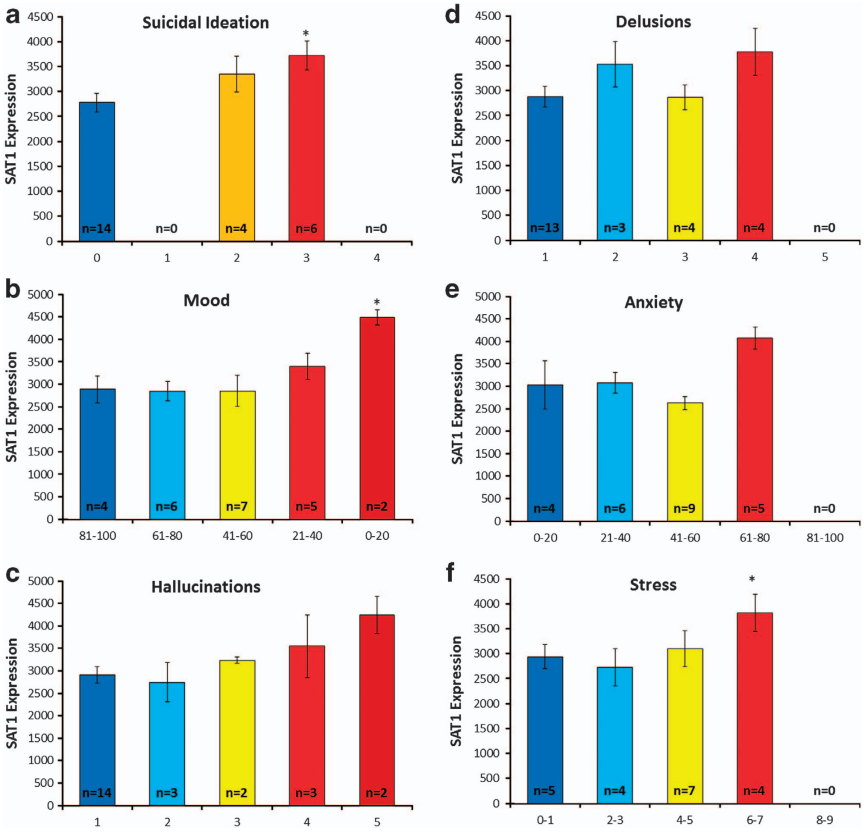


Figure 4. SAT1 (spermidine/spermine N1–acetyltransferase 1) expression in the bipolar discovery cohort: relationship with suicidal ideation (SI), mood, psychosis, anxiety and stress. (**a**) SAT1 expression and SI item from Hamilton Rating Scale for Depression (HAMD) (scores of 0–4). (**b**) SAT1 expression and visual-analog scale for mood (0–100). High mood is to the left on the *x*-axis, low mood is to the right. (**c**) SAT1 expression and Hallucinations item from Positive and Negative Symptoms Scale (PANSS; scores of 1–7). Higher score indicates higher symptoms. (**d**) SAT1 expression and Delusions item from PANSS (scores of 1–7). Higher score indicates higher symptoms. (**e**) SAT1 expression and visual-analog scale for anxiety (0–100). Higher score indicates higher symptoms. (**f**) SAT1 expression and self-rating scale for stress (1–10). Higher score indicates higher symptoms. Only 20 out of 24 visits had stress data collected. *$P<0.05$ between highest symptoms and lowest symptoms group.

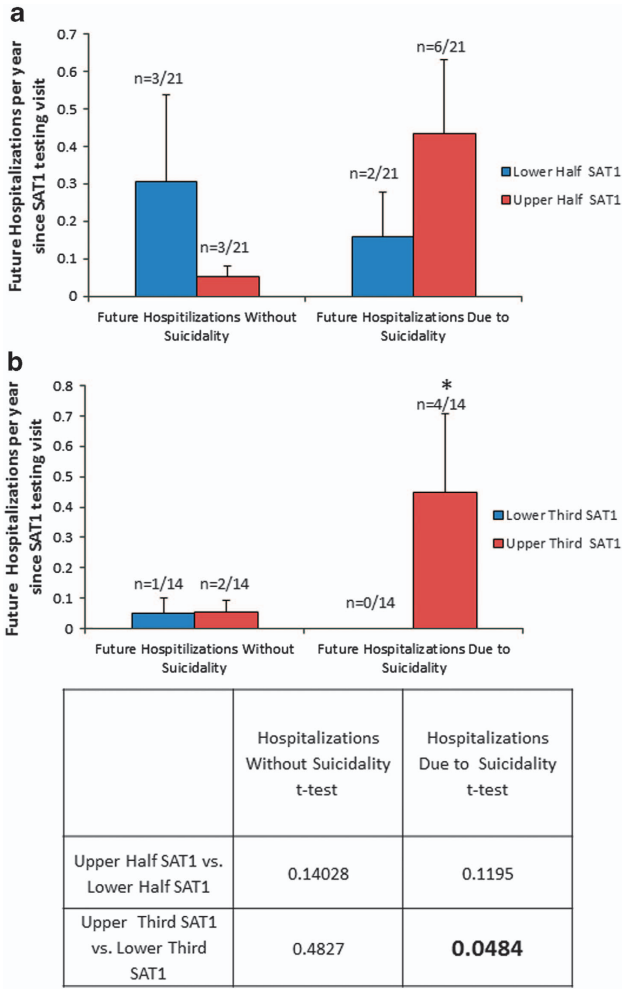
our discovery data sets. Unlike our use of CFG in previous studies, for the current one we did not use any human peripheral tissue evidence from the literature, as there was none directly matching our genes, reflecting perhaps the dearth of peripheral gene expression work done so far on suicides, and the need for a study like ours. We also did not use animal model evidence, as there are to date no clear studies in animal models of self-harm or suicidality. SAT1 was the top-scoring blood biomarker, with the most extensive convergent evidence, increased in suicidal states identified by our work (that is, the top risk marker). CD24 (CD24 molecule/small cell lung carcinoma cluster 4 antigen) was the top blood biomarker decreased in suicidal states (that is, the top protective marker; Figure 2 and Table 2).

Testing in suicide completers

In order to know whether our findings relate to actual completed suicide, we then tested SAT1 levels in the blood samples from a heterogeneous cohort of nine consecutive male suicide completers obtained from the coroner's office, with the following characteristics: we required that the cases included in our analysis had a postmortem interval from last observed alive under 24 h, and that they had committed suicide by means other than overdoses, which could alter gene expression. Remarkably, we found SAT1 gene expression levels to be elevated in nine out of nine (100%) subjects who committed suicide, that we tested. In each of the suicide completers, the increase in SAT1 was at least three s.d. above the average levels in high SI subjects, which constitutes a very stringent threshold for use as a predictive biomarker (Figure 3). We also examined other top candidate biomarkers for suicidality (Figure 3 and Supplementary Figure S3). Remarkably, 13 out of the 41 CFG top-scoring biomarkers from Figure 2b (32%) showed step-wise significant change from no SI to high SI, to the test suicide completers group. Six out of them (15%) remained significant after strict Bonferroni correction for multiple comparisons (Figure 3). The top CFG scoring biomarker SAT1 remained the top biomarker after validation.

Mechanistic understanding

Pathway analyses of our suicidality biomarker data identified among the top pathways the omega-3 docosahexaenoic acid signaling pathway. Low omega-3 levels have been correlated with increased suicidality in human epidemiological studies.[20,21] Several of the biomarkers from our current study (SAT1, S100A8, IL1B and 16 others) were changed in expression by omega-3 treatment in the blood of the circadian clock gene DBP (D-box binding protein) knock-out mouse model in opposite direction to our human suicidality data (Supplementary Table S6). DBP is also one of the biomarkers identified to be decreased in high suicidal states in the current analysis. Serendipitously, previous work by our group has implicated DBP in mood disorders,[22] psychosis,[23] alcoholism[9] and anxiety disorders.[10] Mice engineered to lack DBP were stress-reactive and displayed a behavioral phenotype similar



	Hospitalizations Without Suicidality t-test	Hospitalizations Due to Suicidality t-test
Upper Half SAT1 vs. Lower Half SAT1	0.14028	0.1195
Upper Third SAT1 vs. Lower Third SAT1	0.4827	**0.0484**

Figure 5. Prospective validation of SAT1 (spermidine/spermine N1–acetyltransferase 1): follow-up of future psychiatric hospitalizations due to suicidality. We analyzed in 42 bipolar subjects whether their SAT1 levels at the time of initial testing differentiated those who had subsequent hospitalizations due to suicidality in the years since the testing occurred. Range was 0.33–5.92 years of follow-up, average 2.48 years. (**a**) Upper half of SAT1 scores versus lower half of SAT1 scores. Twenty-one subjects in each group. There were six psychiatric hospitalizations not due to suicidality, and eight psychiatric hospitalizations due to suicidality. (**b**) Upper tertile of SAT1 scores versus lower tertile of SAT1 scores. Fourteen subjects in each group. There were three psychiatric hospitalizations not due to suicidality, and four psychiatric hospitalizations due to suicidality.

to bipolar disorder and comorbid alcoholism.[24] In addition to bipolar disorder, alcoholism increases risk for suicide.[25] Phosphatase and tensin homolog (PTEN), a biomarker increased in suicidality in the current study in the blood, as well as in the brain of suicide completers,[26] was also increased in the amygdala and was decreased in the prefrontal cortex of DBP knock-out mice subjected to stress.[25] S100A8, another biomarker increased in suicidality in the current study, was also increased in the blood of DBP stressed mice. Treatment with omega-3 fatty acids normalized the phenotype of those mice.[27]

Other circadian clock-modulated genes identified by our analysis as biomarkers for suicidality were PIK3R5, MARCKS, IL1B, CASC1, CCRN4L, H3F3B, RBCK1, TNK2 and UBE2B. Circadian genes are involved in sleep–wake cycles, as well as mood regulation.[6,7,22,28,29] Abnormal sleep (insomnia) has been identified as a risk factor for suicide.[30] IL1B is also an inflammatory marker, and has previously been implicated by us in anxiety disorders.[10]

In addition, S100A8, MBNL2 and three other biomarkers had evidence for modulation by clozapine in the blood in opposite direction to our human suicidality data in previous independent animal model pharmacogenomics studies conducted by us[4,23] (Supplementary Table S6). Clozapine is the only FDA-approved treatment for suicidality.[31]

Thus, the convergent evidence for our biomarkers is strong in translational ways beyond those used for their discovery and selection. S100A8 may be a key biomarker to monitor in terms of response to treatment with classic (clozapine) and complementary (omega-3) agents. Other potential drugs to be studied for modulating suicidality were revealed by our analyses (Supplementary Tables S5 and S6).

SAT1, FOXN3, DISC1, MBNL2 and RHEB had genetic association evidence for suicidality, suggesting that they are not only state biomarkers but also trait factors influencing suicidal risk. DISC1 is also one of the top candidate genes for schizophrenia based on a large-scale CFG analysis of schizophrenia genome-wide association study we recently conducted,[11] while DISC1 and MBNL2 are also among of the top candidate genes for bipolar disorder based on a large-scale CFG analysis of bipolar disorder genome-wide association study we previously conducted.[7] In addition, DISC1 has clear animal model data for the role of its interaction with environmental stress in the pathophysiology of psychotic depression.[32] DISC1 and MBNL2 may thus be key state and trait factors for suicidality risk in psychotic mood disorder subjects, and an indication for clozapine treatment in such subjects.

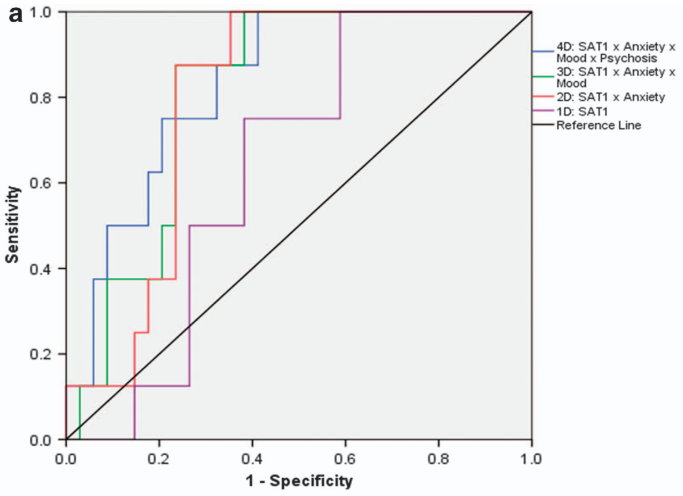
We also looked at the overlap of our suicide biomarkers with our previous mood biomarker[3] and psychosis biomarker[4] work (Supplementary Table S7), as well as with the human postmortem brain literature for other psychiatric disorders (Supplementary Table S8). DOCK5 and four other biomarkers were changed in high suicidal states in the opposite direction to their change in high mood states, and DOCK5 and six other biomarkers were changed in the same direction as their change in high psychosis states, suggesting that suicidality could be viewed as a psychotic dysphoric state, and that DOCK5 may be an additional key biomarker reflecting that state. This molecularly informed view is consistent with the emerging clinical evidence in the field.[33]

The convergence of evidence then suggests that at least in the population we studied, suicidality may be associated with dysphoric mood, as well as increased psychosis, anxiety and stress. In our own data, SAT1 blood gene expression levels showed a trend towards increase in low mood, high psychosis, high anxiety and high stress in our bipolar subjects (Figure 4).

Prospective validation

To further validate SAT1, our top marker, we also looked at subsequent hospitalizations with and without suicidality (Table 1 and Supplementary Table S9), and previous hospitalizations with and without suicidality (Supplementary Table S10), in two live cohorts, one bipolar ($n = 42$) and one psychosis (schizophrenia/schizoaffective; $n = 46$). Higher SAT1 levels compared with lower SAT1 levels at the time of testing differentiated future and past hospitalizations owing to suicidality in the bipolar disorder subjects (Figure 5). A similar but weaker pattern was exhibited in the psychosis (schizophrenia/schizoaffective) subjects (Supplementary Figure S2). Remarkably, besides SAT1, three other (PTEN, MARCKS and MAP3K3) of the six biomarkers that survived Bonferroni correction in the suicide completers cohort validation step also showed similar but weaker results (Supplementary Table S11 and Supplementary Figure S3). Taken together, the prospective and retrospective hospitalization data suggests SAT1,

a



b

D	Test Result Variable(s)	Area Under the Curve	Std. Error	Significance	95% Confidence Interval	
					Lower Bound	Upper Bound
1D	SAT1	0.640	0.086	0.224	.471	.808
2D	SAT1 x Anxiety	0.798	0.068	0.009	.665	.931
3D	SAT1 x Anxiety x Mood	0.813	0.066	0.006	.683	.942
4D	SAT1 x Anxiety x Mood x Psychosis	0.835	0.066	0.004	.706	.964

c

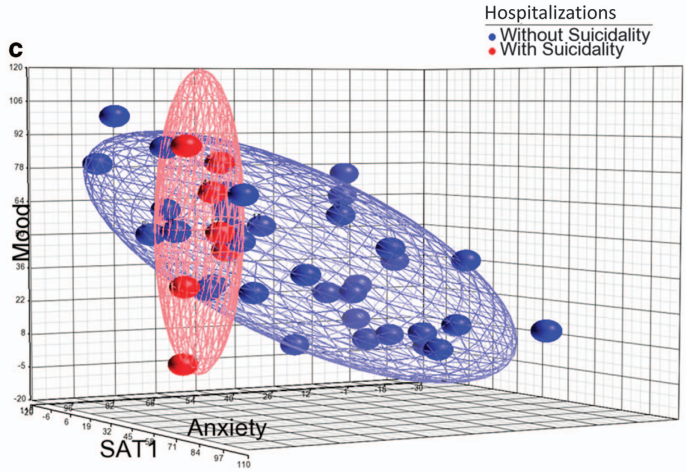


Figure 6. Multi-dimensional prediction of future psychiatric hospitalizations due to suicidality. We analyzed in 42 bipolar subjects whether their SAT1 (spermidine/spermine N1–acetyltransferase 1), anxiety, mood and psychosis levels at the time of initial testing differentiated from those who had subsequent hospitalizations due to suicidality in the years since the testing occurred. Data in each dimension was normalized to a 0–100 scale (with the mood visual-analog scale (VAS) inverted, as the assumption was made that depressed mood states would more closely correlate with suicidality). The angle between dimensions was assumed to be 90°, and a simple Pythagorean distance from origin score was calculated. The distribution of this score in the test cohort was used to generate a receiver-operating characteristic curve for hospitalizations due to suicidality. (**a**) ROC curve. (**b**) Detailed results. (**c**) Three-dimensional visualization.

PTEN, MARCKS and MAP3K3 might be not only state markers but perhaps trait markers as well.

We also examined whether using a multi-dimensional approach enhanced our ability to predict future hospitalizations, by adding data about mood, anxiety and psychosis to the data about the SAT1 expression levels (Figure 6). We found that the receiver-operating characteristic curve improved in a step-wise fashion, from an area under the curve of 0.640 with SAT1 alone, to an area under the curve of 0.798 with SAT1 and anxiety, area under the curve of 0.813 with SAT1, anxiety and mood, and area under the curve of 0.835 with SAT1, anxiety, mood and psychosis. From our preliminary work, we identified levels of SAT1 that provide different levels of sensitivity and specificity (Supplementary Table S12). The anxiety and mood information was obtained from simple visual-analog scales, previously described by us.[34] The psychosis information is based on the combining of the scores on the hallucinations and delusions in the Positive and Negative Symptoms Scale (Supplementary Figure S5). Of note, this simple clinical–genomic approach does not directly ask about SI, which some individuals may deny or choose not to share with clinicians. Similar data were obtained for the panel of six top markers as shown in Supplementary Figure S6.

DISCUSSION

Using discovery in live subjects and validation in suicide completers, we found possible biomarkers for suicidality. Our top biomarker finding, SAT1, as well as PTEN, MARCKS and MAP3K3, were additionally validated by prospective and retrospective analyses in live subjects, looking at the ability to predict and differentiate future and past hospitalizations due to suicidality in bipolar disorder and psychosis (schizophrenia/schizoaffective; Supplementary Table S11).

Apoptosis

Beyond predictions, as a window into the biology of suicidality, the current work shows overlap at a gene and pathway level with apoptosis (Table 3, Supplementary Table S3 and S4). SAT1, for example, is a key catabolic enzyme for polyamines. Polyamine levels within cells control cell viability, and significant decreases in polyamine levels can result in apoptosis.[35] They seem to reflect an endowment for cellular and organismal activity and growth, key characteristics of mood.[3,7,36] SAT1, which is increased in live SI subjects and in suicide completers in our studies, is highly inducible by a variety of stimuli, including toxins, cytokines, heat shock, ischemia and other stresses. SAT1-overexpressing mice had alterations in their polyamine pool, hair loss, infertility and weight loss.[37,38] Turecki and colleagues[39] have provided compelling evidence for changes in the polyamine system in the brain of suicide completers. CD24, our top biomarker decreased in suicidal subjects, also has roles in apoptosis. Mice lacking CD24 show an increased rate of apoptosis.[40] It could be that simpler mechanisms related to cellular survival and programed cell-death decision have been recruited by evolution for higher mental functions, such as feelings, thoughts, actions and behaviors, leading to suicidality. In that sense, suicidality could be viewed as whole-organism apoptosis ('self-poptosis'). Apoptosis mechanisms have previously been implicated in mood disorders, and their inhibition in affective resilience.[41] Interestingly, lithium, a medication with clinical evidence for preventing suicidality in bipolar disorder,[42] has anti-apoptotic effects at a cellular level.[43] Imaging studies have shown reduced gray matter volume in the brain of individuals with bipolar disorder and history of suicide attempts. Long-term lithium treatment was associated with increased gray matter volumes in the same areas where suicide was associated with decreased gray matter.[44]

Conclusions and future directions

Taken together, our results have implications for the understanding of suicide, as well as for the development of objective laboratory tests and tools to track suicidal risk and response to treatment. First, our results open empirical avenues for future field trials, clinical testing and validation in various at-risk populations, including studies in individuals with major depressive disorder. The current work was based on subjects with bipolar disorder, psychosis (schizophrenia/schizoaffective disorder) and coroner's office cases, which may represent a more externalizing or impulsive population and type of suicidality. Other types are likely to exist. Second, more work also needs to be done to examine potential gender and ethnicity differences. Our current work is based on male Caucasian subjects. Third, predicting suicidal feelings and thoughts (ideation) may be different than predicting suicidal actions and behaviors. Our current work has focused on suicide completers and hospitalizations, admittedly a more emergent concern. Fourth, state versus trait issues and sensitivity versus specificity for suicidality, for the individual markers identified by us, as well as for panels of markers and multi-modal approaches, need to be studied more extensively in different populations. Fifth, past individual and family history, as well as environmental context, may help improve predictive approaches. Our approach was very focused and reductionist, albeit with good results.

Given the fact that approximately one million people die of suicide worldwide each year, and this is a potentially preventable cause of death, the need for, urgency and importance of efforts such as ours cannot be overstated.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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This work is, in essence, a field-wide collaboration. We would like to acknowledge our debt of gratitude for the efforts and results of the many other groups, cited in our paper, who have conducted and published studies (genetic and gene expression) in suicidality. With their arduous and careful work, a convergent approach, such as ours, is possible. We would particularly like to thank the veterans and other subjects who volunteered to participate in these studies, their families and their caregivers. Without their generous contribution, such work to advance the understanding of mental illness and help others would not be possible. We would like to thank Terri Gelbart for excellent technical help on the microarray work, and Dawn Graham for help with the human subjects data. This work was supported by an NIH Directors' New Innovator Award (1DP2OD007363) and a VA Merit Award (1I01CX000139-01) to ABN.

AUTHOR CONTRIBUTIONS

ABN designed the study and wrote the manuscript. HLN, DFL and MA analyzed the data. LP, LMG, NJ, EW, SB and GS performed database work. EB, KO, HD, JV, RS and MR organized and conducted testing in bipolar disorder subjects. MY, AB, AS and GES organized and carried out postmortem sample collections. NJS, SMK and DRS conducted microarray experiments and provided input on data analyses. All authors discussed the results and commented on the manuscript.

REFERENCES

1 Nock MK, Borges G, Bromet EJ, Cha CB, Kessler RC, Lee S. Suicide and suicidal behavior. *Epidemiol Rev* 2008; **30**: 133–154.
2 Berngruber TW, Lion S, Gandon S. Evolution of suicide as a defence strategy against pathogens in a spatially structured environment. *Ecol Lett* 2013; **16**: 446–453.
3 Le-Niculescu H, Kurian SM, Yehyawi N, Dike C, Patel SD, Edenberg HJ *et al.* Identifying blood biomarkers for mood disorders using convergent functional genomics. *Mol Psychiatr* 2009; **14**: 156–174.
4 Kurian SM, Le-Niculescu H, Patel SD, Bertram D, Davis J, Dike C *et al.* Identification of blood biomarkers for psychosis using convergent functional genomics. *Mol Psychiatr* 2011; **16**: 37–58.
5 Niculescu A, Segal D, Kuczenski R, Barrett T, Hauger R, Kelsoe J. Identifying a series of candidate genes for mania and psychosis: a convergent functional genomics approach. *Physiol Genomics* 2000; **4**: 83–91.
6 Ogden CA, Rich ME, Schork NJ, Paulus MP, Geyer MA, Lohr JB *et al.* Candidate genes, pathways and mechanisms for bipolar (manic-depressive) and related disorders: an expanded convergent functional genomics approach. *Mol Psychiatr* 2004; **9**: 1007–1029.
7 Patel SD, Le-Niculescu H, Koller DL, Green SD, Lahiri DK, McMahon FJ *et al.* Coming to grips with complex disorders: genetic risk prediction in bipolar disorder using panels of genes identified through convergent functional genomics. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**: 850–877.
8 Le-Niculescu H, Patel SD, Bhat M, Kuczenski R, Faraone SV, Tsuang MT *et al.* Convergent functional genomics of genome-wide association data for bipolar disorder: comprehensive identification of candidate genes, pathways and mechanisms. *Am J Med Genet B Neuropsychiatr Genet* 2009; **150B**: 155–181.
9 Rodd ZA, Bertsch BA, Strother WN, Le-Niculescu H, Balaraman Y, Hayden E *et al.* Candidate genes, pathways and mechanisms for alcoholism: an expanded convergent functional genomics approach. *Pharmacogenomics J* 2007; **7**: 222–256.
10 Le-Niculescu H, Balaraman Y, Patel SD, Ayalew M, Gupta J, Kuczenski R *et al.* Convergent functional genomics of anxiety disorders: translational identification of genes, biomarkers, pathways and mechanisms. *Transl Psychiatr* 2011; **1**: e9.
11 Ayalew M, Le-Niculescu H, Levey DF, Jain N, Changala B, Patel SD *et al.* Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction. *Mol Psychiatr* 2012; **17**: 887–905.

12 Niculescu AB, Le-Niculescu H. Convergent Functional Genomics: what we have learned and can learn about genes, pathways, and mechanisms. *Neuropsychopharmacology* 2010; **35**: 355–356.
13 Novick DM, Swartz HA, Frank E. Suicide attempts in bipolar I and bipolar II disorder: a review and meta-analysis of the evidence. *Bipolar Disord* 2010; **12**: 1–9.
14 Chen R, Mias GI, Li-Pook-Than J, Jiang L, Lam HY, Miriami E *et al.* Personal omics profiling reveals dynamic molecular and medical phenotypes. *Cell* 2012; **148**: 1293–1307.
15 Sequeira A, Morgan L, Walsh DM, Cartagena PM, Choudary P, Li J *et al.* Gene expression changes in the prefrontal cortex, anterior cingulate cortex and nucleus accumbens of mood disorders subjects that committed suicide. *PloS One* 2012; **7**: e35367.
16 Karege F, Perroud N, Burkhardt S, Schwald M, Ballmann E, La Harpe R *et al.* Alteration in kinase activity but not in protein levels of protein kinase B and glycogen synthase kinase-3beta in ventral prefrontal cortex of depressed suicide victims. *Biol Psychiatry* 2007; **61**: 240–245.
17 Bertsch B, Ogden CA, Sidhu K, Le-Niculescu H, Kuczenski R, Niculescu AB. Convergent functional genomics: a Bayesian candidate gene identification approach for complex disorders. *Methods* 2005; **37**: 274–279.
18 Le-Niculescu H, McFarland MJ, Mamidipalli S, Ogden CA, Kuczenski R, Kurian SM *et al.* Convergent Functional Genomics of bipolar disorder: from animal model pharmacogenomics to human genetics and biomarkers. *Neurosci Biobehav Rev* 2007; **31**: 897–903.
19 Le-Niculescu H, Patel SD, Niculescu AB. Convergent integration of animal model and human studies of bipolar disorder (manic-depressive illness). *Curr Opin Pharmacol* 2010; **10**: 594–600.
20 Sublette ME, Hibbeln JR, Galfalvy H, Oquendo MA, Mann JJ. Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. *Am J Psychiatry* 2006; **163**: 1100–1102.
21 Lewis MD, Hibbeln JR, Johnson JE, Lin YH, Hyun DY, Loewke JD. Suicide deaths of active-duty US military and omega-3 fatty-acid status: a case-control comparison. *J Clin Psychiatry* 2011; **72**: 1585–1590.
22 Niculescu 3rd AB, Segal DS, Kuczenski R, Barrett T, Hauger RL, Kelsoe JR. Identifying a series of candidate genes for mania and psychosis: a convergent functional genomics approach. *Physiol Genomics* 2000; **4**: 83–91.
23 Le-Niculescu H, Balaraman Y, Patel S, Tan J, Sidhu K, Jerome RE *et al.* Towards understanding the schizophrenia code: an expanded convergent functional genomics approach. *Am J Med Genet B Neuropsychiatr Genet* 2007; **144B**: 129–158.
24 Le-Niculescu H, McFarland MJ, Ogden CA, Balaraman Y, Patel S, Tan J *et al.* Phenomic, convergent functional genomic, and biomarker studies in a stress-reactive genetic animal model of bipolar disorder and co-morbid alcoholism. *Am J Med Genet B Neuropsychiatr Genet* 2008; **147B**: 134–166.
25 Oquendo MA, Currier D, Liu SM, Hasin DS, Grant BF, Blanco C. Increased risk for suicidal behavior in comorbid bipolar disorder and alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Clin Psychiatry* 2010; **71**: 902–909.
26 Dwivedi Y, Rizavi HS, Zhang H, Roberts RC, Conley RR, Pandey GN. Modulation in activation and expression of phosphatase and tensin homolog on chromosome ten, Akt1, and 3-phosphoinositide-dependent kinase 1: further evidence demonstrating altered phosphoinositide 3-kinase signaling in postmortem brain of suicide subjects. *Biol Psychiatry* 2010; **67**: 1017–1025.
27 Le-Niculescu H, Case NJ, Hulvershorn L, Patel SD, Bowker D, Gupta J *et al.* Convergent functional genomic studies of omega-3 fatty acids in stress reactivity, bipolar disorder and alcoholism. *Transl Psychiatry* 2011; **1**: e4.
28 McGrath CL, Glatt SJ, Sklar P, Le-Niculescu H, Kuczenski R, Doyle AE *et al.* Evidence for genetic association of RORB with bipolar disorder. *BMC Psychiatry* 2009; **9**: 70.
29 Bunney BG, Bunney WE. Mechanisms of Rapid Antidepressant Effects of Sleep Deprivation Therapy: Clock Genes and Circadian Rhythms. *Biol Psychiatry* 2012; **73**: 1164–1171.
30 McCall WV, Batson N, Webster M, Case LD, Joshi I, Derreberry T *et al.* Nightmares and Dysfunctional Beliefs about Sleep Mediate the Effect of Insomnia Symptoms on Suicidal Ideation. *J Clin Sleep Med* 2013; **9**: 135–140.
31 Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A *et al.* Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003; **60**: 82–91.
32 Niwa M, Jaaro-Peled H, Tankou S, Seshadri S, Hikida T, Matsumoto Y *et al.* Adolescent stress-induced epigenetic control of dopaminergic neurons via glucocorticoids. *Science* 2013; **339**: 335–339.
33 Kelleher I, Lynch F, Harley M, Molloy C, Roddy S, Fitzpatrick C *et al.* Psychotic symptoms in adolescence inex risk for suicidal behavior: findings from 2 population-based case-control clinical interview studies. *Arch Gen Psychiatry* 2012; **69**: 1277–1283.
34 Niculescu AB, Lulow LL, Ogden CA, Le-Niculescu H, Salomon DR, Schork NJ *et al.* PhenoChipping of psychotic disorders: a novel approach for deconstructing and quantitating psychiatric phenotypes. *Am J Med Genet B Neuropsychiatr Genet* 2006; **141B**: 653–662.
35 Schipper RG, Penning LC, Verhofstad AA. Involvement of polyamines in apoptosis. Facts and controversies: effectors or protectors? *Semin Cancer Biol* 2000; **10**: 55–68.
36 Niculescu 3rd AB, Schork NJ, Salomon DR. Mindscape: a convergent perspective on life, mind, consciousness and happiness. *J Affect Disord* 2010; **123**: 1–8.
37 Pietila M, Alhonen L, Halmekyto M, Kanter P, Janne J, Porter CW. Activation of polyamine catabolism profoundly alters tissue polyamine pools and affects hair growth and female fertility in transgenic mice overexpressing spermidine/spermine N1-acetyltransferase. *J Biol Chem* 1997; **272**: 18746–18751.
38 Min SH, Simmen RC, Alhonen L, Halmekyto M, Porter CW, Janne J *et al.* Altered levels of growth-related and novel gene transcripts in reproductive and other tissues of female mice overexpressing spermidine/spermine N1-acetyltransferase (SSAT). *J Biol Chem* 2002; **277**: 3647–3657.
39 Fiori LM, Bureau A, Labbe A, Croteau J, Noel S, Merette C *et al.* Global gene expression profiling of the polyamine system in suicide completers. *Int J Neuropsychopharmacol* 2011; **14**: 595–605.
40 Duckworth CA, Clyde D, Pritchard DM. CD24 is expressed in gastric parietal cells and regulates apoptosis and the response to Helicobacter felis infection in the murine stomach. *Am J Physioly Gastrointest Liver Physiol* 2012; **303**: G915–G926.
41 Malkesman O, Austin DR, Tragon T, Henter ID, Reed JC, Pellecchia M *et al.* Targeting the BH3-interacting domain death agonist to develop mechanistically unique antidepressants. *Mol Psychiatry* 2012; **17**: 770–780.
42 Tondo L, Baldessarini RJ. Long-term lithium treatment in the prevention of suicidal behavior in bipolar disorder patients. *Epidemiol Psichiatr Soc* 2009; **18**: 179–183.
43 Lowthert L, Leffert J, Lin A, Umlauf S, Maloney K, Muralidharan A *et al.* Increased ratio of anti-apoptotic to pro-apoptotic Bcl2 gene-family members in lithium-responders one month after treatment initiation. *Biol Mood Anxiety Disord* 2012; **2**: 15.
44 Benedetti F, Radaelli D, Poletti S, Locatelli C, Falini A, Colombo C *et al.* Opposite effects of suicidality and lithium on gray matter volumes in bipolar depression. *J Affect Disord* 2011; **135**: 139–147.
45 Fiori LM, Wanner B, Jomphe V, Croteau J, Vitaro F, Tremblay RE *et al.* Association of polyaminergic loci with anxiety, mood disorders, and attempted suicide. *PloS One* 2010; **5**: e15146.
46 Sequeira A, Gwadry FG, Ffrench-Mullen JM, Canetti L, Gingras Y, Casero Jr. RA *et al.* Implication of SSAT by gene expression and genetic variation in suicide and major depression. *Arch Gen Psychiatry* 2006; **63**: 35–48.
47 Chen GG, Fiori LM, Moquin L, Gratton A, Mamer O, Mechawar N *et al.* Evidence of altered polyamine concentrations in cerebral cortex of suicide completers. *Neuropsychopharmacology* 2010; **35**: 1477–1484.
48 Fiori LM, Turecki G. Epigenetic regulation of spermidine/spermine N1-acetyltransferase (SAT1) in suicide. *J Psychiatr Res* 2011; **45**: 1229–1235.
49 Fiori LM, Mechawar N, Turecki G. Identification and characterization of spermidine/spermine N1-acetyltransferase promoter variants in suicide completers. *Biol Psychiatry* 2009; **66**: 460–467.
50 Fiori LM, Zouk H, Himmelman C, Turecki G. X chromosome and suicide. *Mol Psychiatry* 2011; **16**: 216–226.
51 Guipponi M, Deutsch S, Kohler K, Perroud N, Le Gal F, Vessaz M *et al.* Genetic and epigenetic analysis of SSAT gene dysregulation in suicidal behavior. *Am J Med Genet B Neuropsychiatr Genet* 2009; **150B**: 799–807.
52 Klempan TA, Rujescu D, Merette C, Himmelman C, Sequeira A, Canetti L *et al.* Profiling brain expression of the spermidine/spermine N1-acetyltransferase 1 (SAT1) gene in suicide. *Am J Med Genet B Neuropsychiatr Genet* 2009; **150B**: 934–943.
53 Galfalvy H, Zalsman G, Huang YY, Murphy L, Rosoklija G, Dwork AJ *et al.* A pilot genome wide association and gene expression array study of suicide with and without major depression. *World J Biol Psychiatry* 2011 (e-pub ahead of print).
54 Kekesi KA, Juhasz G, Simor A, Gulyassy P, Szego EM, Hunyadi-Gulyas E *et al.* Altered functional protein networks in the prefrontal cortex and amygdala of victims of suicide. *PLoS One* 2012; **7**: e50532.
55 Kim S, Choi KH, Baykiz AF, Gershenfeld HK. Suicide candidate genes associated with bipolar disorder and schizophrenia: an exploratory gene expression profiling analysis of post-mortem prefrontal cortex. *BMC Genomics* 2007; **8**: 413.
56 Klempan TA, Sequeira A, Canetti L, Lalovic A, Ernst C, ffrench-Mullen J *et al.* Altered expression of genes involved in ATP biosynthesis and GABAergic neurotransmission in the ventral prefrontal cortex of suicides with and without major depression. *Mol Psychiatry* 2009; **14**: 175–189.

57 Pandey GN, Rizavi HS, Ren X, Fareed J, Hoppensteadt DA, Roberts RC *et al.* Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *J Psychiatr Res* 2012; **46**: 57–63.
58 Lalovic A, Klempan T, Sequeira A, Luheshi G, Turecki G. Altered expression of lipid metabolism and immune response genes in the frontal cortex of suicide completers. *J Affect Disord* 2010; **120**: 24–31.
59 Sequeira A, Klempan T, Canetti L, ffrench-Mullen J, Benkelfat C, Rouleau GA *et al.* Patterns of gene expression in the limbic system of suicides with and without major depression. *Mol Psychiatry* 2007; **12**: 640–655.
60 Zhurov V, Stead JD, Merali Z, Palkovits M, Faludi G, Schild-Poulter C *et al.* Molecular pathway reconstruction and analysis of disturbed gene expression in depressed individuals who died by suicide. *PLoS One* 2012; **7**: e47581.
61 Freemantle E, Mechawar N, Turecki G. Cholesterol and phospholipids in frontal cortex and synaptosomes of suicide completers: relationship with endosomal lipid trafficking genes. *J Psychiatr Res* 2013; **47**: 272–279.
62 Pandey GN, Dwivedi Y, Ren X, Rizavi HS, Roberts RC, Conley RR *et al.* Altered expression and phosphorylation of myristoylated alanine-rich C kinase substrate (MARCKS) in postmortem brain of suicide victims with or without depression. *J Psychiatr Res* 2003; **37**: 421–432.
63 Menke A, Domschke K, Czamara D, Klengel T, Hennings J, Lucae S *et al.* Genome-wide association study of antidepressant treatment-emergent suicidal ideation. *Neuropsychopharmacology* 2012; **37**: 797–807.
64 Butler AW, Breen G, Tozzi F, Craddock N, Gill M, Korszun A *et al.* A genome-wide linkage study on suicidality in major depressive disorder confirms evidence for linkage to 2p12. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**: 1465–1473.

Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

Supplementary Information:

Table S1. Psychiatric medications of subjects in the live bipolar discovery cohort.

SubjectID-Visit	Psychiatric Medications
phchp023v1	FLEXARIL 10MG FOR SLEEP PRN LAMOTRIGINE 200MG ZIPRASIDONE 60MG
v2	FLEXARIL 10MG FOR SLEEP PRN LAMOTRIGINE 200MG ZIPRASIDONE 60MG
v3	FLEXARIL 10MG FOR SLEEP PRN LAMOTRIGINE 200MG ZIPRASIDONE 60MG
phchp093v1	CITALOPRAM HYDROBROMIDE 40MG TAB TAKE ONE-HALF TABLET ORALLY EVERY DAY VALPROIC ACID 500MG 24HR (ER) SA TAB TAKE THREE TABLETS ORALLY AT BEDTIME FOR MOOD. QUETIAPINE FUMARATE 100MG TAB TAKE ONE TABLET ORALLY AT BEDTIME FOR SLEEP AND MOOD. GABAPENTIN 300MG CAP TAKE ONE CAPSULE ORALLY AT BEDTIME FOR 3 DAYS, THEN TAKE ONE CAPSULE , TWICE A DAY FOR LEG PAIN QUETIAPINE FUMARATE 25MG TAB TAKE ONE TABLET ORALLY EVERY DAY AS NEEDED TAKE FOR VOICES
v2	CITALOPRAM HYDROBROMIDE 40MG TAB TAKE ONE-HALF TABLET ORALLY EVERY DAY FOR DEPRESSION VALPROIC ACID 500MG 24HR (ER) SA TAB TAKE THREE TABLETS ORALLY AT BEDTIME FOR MOOD DOXEPIN HCL 10MG CAP TAKE ONE CAPSULE ORALLY AT BEDTIME FOR NEUROPATHIC PAIN GABAPENTIN 300MG CAP TAKE TWO CAPSULES ORALLY TWICE A DAY AND TAKE THREE CAPSULES AT BEDTIME QUETIAPINE FUMARATE 100MG TAB TAKE ONE TABLET ORALLY AT BEDTIME QUETIAPINE FUMARATE 25MG TAB TAKE ONE TABLET ORALLY EVERY DAY TAKE FOR VOICES
v3	CITALOPRAM HYDROBROMIDE 40MG TAB TAKE ONE-HALF TABLET ORALLY EVERY DAY FOR DEPRESSION VALPROIC ACID 500MG 24HR (ER) SA TAB TAKE THREE TABLETS ORALLY AT BEDTIME FOR MOOD

	DOXEPIN HCL 10MG CAP TAKE ONE CAPSULE ORALLY AT BEDTIME FOR NEUROPATHIC PAIN GABAPENTIN 300MG CAP TAKE TWO CAPSULES ORALLY TWICE A DAY WITH FOOD QUETIAPINE FUMARATE 100MG TAB TAKE ONE TABLET ORALLY PENDING AT BEDTIME QUETIAPINE FUMARATE 25MG TAB TAKE ONE TABLET ORALLY EVERY DAY TAKE FOR VOICES
phchp095v1	BENZTROPINE MESYLATE ORAL 1MG TAB TAKE ONE TABLET ORALLY TWICE A DAY FOR RESTLESSNESS, ANXIETY BUPROPRION 150MG TAB TAKE ONE TABLET ORALLY DAILY RISPERIDONE 4MG TAB TAKE ONE TABLET ORALLY EVERY DAY
v2	BENZTROPINE MESYLATE ORAL 1MG TAB TAKE ONE TABLET ORALLY TWICE A DAY FOR RESTLESSNESS, ANXIETY TRAZODONE100MG TAB TAKE ONE TABLET ORALLY AT BEDTIME AS NEEDED FOR INSOMNIA RISPERIDONE 4MG TAB TAKE ONE TABLET ORALLY EVERY DAY
v3	BENZTROPINE MESYLATE ORAL 1MG TAB TAKE ONE TABLET ORALLY TWICE A DAY FOR RESTLESSNESS, ANXIETY TRAZODONE100MG TAB TAKE ONE TABLET ORALLY AT BEDTIME AS NEEDED FOR INSOMNIA RISPERIDONE 4MG TAB TAKE ONE TABLET ORALLY EVERY DAY LORAZEPAM INJ IM Q4H PRN 2MG/1ML LORAZEPAM TAB PO Q6H PRN 2MG
phchp122v1	VALPROIC ACID 500MG 24HR (ER) SA TAB TAKE TWO TABLETS ORALLY AT BEDTIME FOR IMPULSES/MOOD STABILIZATION LORAZEPAM 1MG TAB TAKE TWO TABLETS ORALLY AT BEDTIME AS NEEDED FOR INSOMNIA MIRTAZAPINE 30MG TAB TAKE ONE TABLET ORALLY AT BEDTIME FOR MAJOR DEPRESSION. PRAZOSIN 2MG CAP TAKE ONE CAPSULE ORALLY TWICE A DAY FOR NIGHTMARES AND FOR URINE FLOW. TAKE SECOND DOSE AT BEDTIME. VENLAFAXINE HCL 150MG 24HR SA TAB TAKE ONE TABLET ORALLY TWICE A DAY (BREAKFAST AND LUNCH) FOR MAJOR DEPRESSION ZIPRASIDON 80MG CAP TAKE TWO CAPSULES ORALLY EVERY EVENING WITH DINNER FOR MOOD STABLIZATION.
v2	VALPROIC ACID 500MG 24HR (ER) SA TAB TAKE TWO TABLETS ORALLY AT BEDTIME FOR IMPULSES/MOOD STABILIZATION LORAZEPAM 1MG TAB TAKE TWO TABLETS ORALLY AT BEDTIME AS NEEDED FOR INSOMNIA MIRTAZAPINE 30MG TAB TAKE ONE TABLET ORALLY AT BEDTIME FOR MAJOR DEPRESSION. PRAZOSIN 2MG CAP TAKE ONE CAPSULE ORALLY TWICE A DAY FOR NIGHTMARES AND FOR URINE FLOW. TAKE SECOND DOSE AT BEDTIME.

	VENLAFAXINE HCL 150MG 24HR SA TAB TAKE ONE TABLET ORALLY TWICE A DAY (BREAKFAST AND LUNCH) FOR MAJOR DEPRESSION ZIPRASIDON 80MG CAP TAKE TWO CAPSULES ORALLY EVERY EVENING WITH DINNER FOR MOOD STABLIZATION.
phchp128v1	DISULFIRAM 250MG TAB TAKE ONE TABLET ORALLY EVERY DAY VALPROIC ACID 500MG 24HR (ER) SA TAB TAKE THREE TABLETS ORALLY AT BEDTIME FOR MOOD STABILIZATION. TRAZODONE50MG TAB TAKE ONE TABLET ORALLY AT BEDTIME AS NEEDED FOR INSOMNIA
v2	DISULFIRAM 250MG TAB TAKE ONE TABLET ORALLY EVERY DAY VALPROIC ACID 500MG 24HR (ER) SA TAB TAKE THREE TABLETS ORALLY AT BEDTIME FOR MOOD STABILIZATION. TRAZODONE50MG TAB TAKE ONE TABLET ORALLY AT BEDTIME AS NEEDED FOR INSOMNIA
phchp136v1	BENZTROPINE MESYLATE ORAL MESYLATE 1MG TAB TAKE ONE TABLET ORALLY TWICE A DAY FOR ABNORMAL MOVEMENTS CHLORPROMAZINE 100MG TAB TAKE ONE TABLET ORALLY AT BEDTIME HALOPERIDOL DECANOATE 5ML(100MG/ML) INJ INJECT 200 MG HOLD (2ML) INTRAMUSCULAR EVERY 4 WEEKS OXCARBAZEPINE 300MG TAB TAKE ONE TABLET ORALLY EVERY MORNING AND TAKE THREE TABLETS AT BEDTIME FOR MOOD STABILIZATION FISH OIL CAP/TAB
v2	BENZTROPINE MESYLATE ORAL MESYLATE 2MG TAB TAKE ONE TABLET ORALLY TWICE A DAY FOR ABNORMAL MOVEMENTS CHLORPROMAZINE 100MG TAB TAKE ONE TABLET ORALLY AT BEDTIME HALOPERIDOL DECANOATE 5ML(100MG/ML) INJ INJECT 200 MG HOLD (2ML) INTRAMUSCULAR EVERY 4 WEEKS OXCARBAZEPINE 300MG TAB TAKE ONE TABLET ORALLY EVERY MORNING AND TAKE THREE TABLETS AT BEDTIME FOR MOOD STABILIZATION
v3	BENZTROPINE MESYLATE ORAL MESYLATE 2MG TAB TAKE ONE TABLET ORALLY TWICE A DAY FOR ABNORMAL MOVEMENTS CHLORPROMAZINE 100MG TAB TAKE ONE TABLET ORALLY AT BEDTIME HALOPERIDOL DECANOATE 5ML(100MG/ML) INJ INJECT 200 MG HOLD(2ML) INTRAMUSCULAR EVERY 4 WEEKS OXCARBAZEPINE 300MG TAB TAKE ONE TABLET ORALLY EVERY MORNING AND TAKE THREE TABLETS AT BEDTIME FOR MOOD STABILIZATION
phchp153v1	TRAZODONE50MG TAB TAKE ONE TO ONE AND ONE-HALF TABLETS ORALLY AT BEDTIME FOR IN ABLILITY TO SLEEP. VENLAFAXINE HCL 225MG 24HR SA TAB TAKE ONE TABLET ORALLY EVERY DAY WITH BREAKFAST FOR DEPRESSION AND ANXIETY
v2	TRAZODONE100MG TAB TAKE ONE TABLET ORALLY AT BEDTIME FOR INABILITY TO SLEEP VENLAFAXINE HCL 225MG 24HR SA TAB TAKE ONE TABLET ORALLY EVERY DAY WITH BREAKFAST FOR DEPRESSION AND ANXIETY
v3	VENLAFAXINE HCL 150 mg 24 hr SA tab – 1x per day

	TRAZADONE HCL 50 mg – 1x per day
phchp179v1	LISDEXAMFETAMINE (40 mg) QUETIAPINE (600 mg) PAROXETINE (30 mg) ALPRAZOLAM (1/2 mg per night) ZOLPIDEM (10 mg per night)
v2	No Psychiatric Medications
v3	QUETIAPINE 100 mg – is being tapered off ZIPRASIDONE 120 mg PAROXETINE 30 mg ALPRAZOLAM unknown dosage, PRN LISDEXAMFETAMINE 50 mg
phchp183v1	ARIPIPRAZOLE TAB 20MG PO DAILY BENZTROPINE MESYLATE ORAL TAB 1MG PO Q4H PRN FOR EPS SYMPTOMS VALPROIC ACID TAB,SA,24HR (EXTENDED 2000MG PO BEDTIME HALOPERIDOL INJ,SOLN 5 MG IM Q4H PRN FOR AGITATION HALOPERIDOL TAB 5MG PO Q4H PRN Agitation LORAZEPAM INJ 2MG/1ML IM Q4H PRN Agitation RISPERIDONE TAB 1MG PO BID HYDROXYZINE PAMOATE 25MG CAP TAKE ONE CAPSULE ORALLY EVERY 6 HOURS AS NEEDED FOR ANXIETY FISH OIL CAP/TAB ORALLY
v2	ARIPIPRAZOLE 20MG TAB TAKE ONE TABLET ORALLY EVERY DAY HYDROXYZINE PAMOATE 25MG CAP TAKE ONE CAPSULE ORALLY EVERY 6 HOURS AS NEEDED FOR ANXIETY CITALOPRAM HYDROBROMIDE 10MG TAB TAKE ONE-HALF TABLET ORALLY EVERY MORNING

Table S2. Toxicology for subjects in the coroner's office test cohort-suicide completers.

SubjectID	Toxicology
INBR009	
INBR011	ALPRAZOLAM 3.2 NG/ML TRAMADOL 331 NG/ML NORTRAMADOL 179 NG/ML BUPROPION 136 NG/ML CITALOPRAM/ESCITALOPRAM 229 NG/ML CAFFEINE POSITIVE COTININE POSITIVE
INBR012	Not Available
INBR013	CAFFEINE POSITIVE
INBR014	ETHANOL 0.15 % (W/V) CAFFEINE
INBR015	ETHANOL 0.119 % (W/V) CAFFEINE
INBR016	Not Available
INBR017	Not Available
INBR018	ETHANOL 0.057 %(W/V) AMIODARONE CAFFEINE COTININE

Table S3. Complete list of genes differentially expressed in the discovery cohort overlapping between the intra-subject and inter-subject analyses (n=246).

Probeset ID	Gene Symbol	Gene Name	Change	Total CFG Score	Evidence for possible roles in apoptosis
203455_s_at	SAT1	spermidine/spermine N1-acetyltransferase 1	I	8	yes
209772_s_at	CD24	CD24 molecule	D	8	yes
230790_x_at	FOXN3	forkhead box N3	I	8	
231577_s_at; 202269_x_at; 202270_at	GBP1	guanylate binding protein 1, interferon-inducible	I	8	yes
227553_at	PIK3R5	phosphoinositide-3-kinase, regulatory subunit 5	I	8	
221653_x_at	APOL2	apolipoprotein L, 2	I	6	
218608_at	ATP13A2	ATPase type 13A2	D	6	
214149_s_at	ATP6V0E1	ATPase, H+ transporting, lysosomal 9kDa, V0 subunit e1	I	6	
202017_at	EPHX1	epoxide hydrolase 1, microsomal (xenobiotic)	D	6	yes
239099_at	GCOM1	GRINL1A complex locus 1	I	6	
201185_at	HTRA1	HtrA serine peptidase 1	D	6	yes
39402_at	IL1B	interleukin 1, beta	I	6	yes
211354_s_at	LEPR	leptin receptor	D	6	yes
218656_s_at	LHFP	lipoma HMGIC fusion partner	I	6	
236156_at	LIPA	lipase A, lysosomal acid, cholesterol esterase	I	6	
213002_at	MARCKS	myristoylated alanine-rich protein kinase C substrate	I	6	yes
230699_at	PGLS	6-phosphogluconolactonase	I	6	
222176_at	PTEN	phosphatase and tensin homolog	I	6	yes
216153_x_at	RECK	reversion-inducing-cysteine-rich protein with kazal motifs	I	6	yes
200671_s_at	SPTBN1	spectrin, beta, non-erythrocytic 1	D	6	yes
202688_at	TNFSF10	tumor necrosis factor (ligand) superfamily, member 10	I	6	yes
203504_s_at; 203505_at	ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	I	4	
241631_at	ARHGEF40	Rho guanine nucleotide exchange factor (GEF) 40	I	4	
220168_at	CASC1	cancer susceptibility candidate 1	I	4	
219799_s_at	DHRS9	dehydrogenase/reductase (SDR family) member 9	I	4	
244642_at	DISC1	disrupted in schizophrenia 1	I	4	
204211_x_at	EIF2AK2	eukaryotic translation initiation factor 2-alpha kinase 2	I	4	yes
231247_s_at	LOC727820	uncharacterized LOC727820	I	4	

242117_at	MAP3K3	mitogen-activated protein kinase kinase kinase 3	I	4	yes
205017_s_at	MBNL2	muscleblind-like splicing regulator 2	D	4	
1553575_at	MT-ND6	mitochondrially encoded NADH dehydrogenase 6	I	4	
217334_at	OR2J3	olfactory receptor, family 2, subfamily J, member 3	D	4	
1565597_at	RBM47	RNA binding motif protein 47	I	4	
227633_at	RHEB	Ras homolog enriched in brain	D	4	yes
228248_at	RICTOR	RPTOR independent companion of MTOR, complex 2	I	4	
243271_at; 230036_at	SAMD9L	sterile alpha motif domain containing 9-like	I	4	
206995_x_at	SCARF1	scavenger receptor class F, member 1	I	4	
213119_at	SLC36A1	solute carrier family 36 (proton/amino acid symporter), member 1	I	4	
232375_at	STAT1	signal transducer and activator of transcription 1, 91kDa	I	4	yes
236879_at	UBA6	ubiquitin-like modifier activating enzyme 6	I	4	
1563075_s_at	ZC3HAV1	zinc finger CCCH-type, antiviral 1	I	4	
213736_at	COX5B	cytochrome c oxidase subunit Vb	I	3	
203874_s_at	SMARCA1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 1	I	3	
229577_at	AGPAT6	1-acylglycerol-3-phosphate O-acyltransferase 6 (lysophosphatidic acid acyltransferase, zeta)	D	2	
206513_at	AIM2	absent in melanoma 2	I	2	yes
227438_at	ALPK1	alpha-kinase 1	I	2	
210873_x_at	APOBEC3A	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A	I	2	
239002_at	ASPM	asp (abnormal spindle) homolog, microcephaly associated (Drosophila)	D	2	
222840_at	ATG2B	autophagy related 2B	D	2	
220237_at	ATG3	autophagy related 3	I	2	
211852_s_at	ATRN	attractin	D	2	
243839_s_at	ATXN2	ataxin 2	I	2	yes
204516_at	ATXN7	ataxin 7	I	2	
203140_at; 228758_at	BCL6	B-cell CLL/lymphoma 6	I	2	yes
219072_at	BCL7C	B-cell CLL/lymphoma 7C	D	2	
214068_at	BEAN1	brain expressed, associated with NEDD4, 1	D	2	
212563_at	BOP1	block of proliferation 1	D	2	
233809_at	C15orf63	chromosome 15 open reading frame 63	I	2	yes
221954_at	C20orf111	chromosome 20 open reading frame 111	I	2	yes
1564276_at	C5orf56	chromosome 5 open reading frame 56	I	2	
1553329_at	C7orf45	chromosome 7 open reading frame 45	I	2	
227364_at	CAPZA1	capping protein (actin filament) muscle Z-line, alpha 1	I	2	yes
213596_at	CASP4	caspase 4, apoptosis-related cysteine peptidase	I	2	yes
207500_at	CASP5	caspase 5, apoptosis-related cysteine peptidase	I	2	yes

205099_s_at	CCR1	chemokine (C-C motif) receptor 1	I	2	yes
1554283_at	CCRN4L	CCR4 carbon catabolite repression 4-like (S. cerevisiae)	I	2	
206485_at	CD5	CD5 molecule	D	2	yes
243931_at	CD58	CD58 molecule	I	2	yes
211189_x_at	CD84	CD84 molecule	D	2	
234255_at	CDC42SE2	CDC42 small effector 2	I	2	
209498_at	CEACAM1	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)	I	2	yes
224198_at	CELA1	chymotrypsin-like elastase family, member 1	D	2	
210069_at	CHKB-CPT1B	CHKB-CPT1B readthrough (non-protein coding)	I	2	
222174_at	CHURC1-FNTB	CHURC1-FNTB readthrough	D	2	
209571_at	CIR1	corepressor interacting with RBPJ, 1	I	2	
219859_at	CLEC4E	C-type lectin domain family 4, member E	I	2	
221698_s_at	CLEC7A	C-type lectin domain family 7, member A	I	2	yes
200861_at	CNOT1	CCR4-NOT transcription complex, subunit 1	D	2	
211141_s_at	CNOT3	CCR4-NOT transcription complex, subunit 3	D	2	
1569703_a_at	CORO1C	coronin, actin binding protein, 1C	I	2	yes
205624_at	CPA3	carboxypeptidase A3 (mast cell)	I	2	
203532_x_at	CUL5	cullin 5	D	2	yes
202434_s_at	CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	D	2	yes
208281_x_at	DAZ1	deleted in azoospermia 1	I	2	
209782_s_at	DBP	D site of albumin promoter (albumin D-box) binding protein	D	2	yes
218943_s_at	DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	I	2	yes
240358_at	DENND3	DENN/MADD domain containing 3	I	2	
1556769_a_at	DLGAP1	discs, large (Drosophila) homolog-associated protein 1	I	2	
233052_at	DNAH8	dynein, axonemal, heavy chain 8	D	2	yes
223371_s_at	DNAJC4	DnaJ (Hsp40) homolog, subfamily C, member 4	D	2	
237311_at	DOCK1	dedicator of cytokinesis 1	D	2	yes
244840_x_at	DOCK4	dedicator of cytokinesis 4	I	2	
230207_s_at	DOCK5	dedicator of cytokinesis 5	I	2	
225415_at	DTX3L	deltex 3-like (Drosophila)	I	2	
210525_x_at	EFCAB11	EF-hand calcium binding domain 11	I	2	
214313_s_at	EIF5B	eukaryotic translation initiation factor 5B	I	2	
224727_at	EMC10	ER membrane protein complex subunit 10	D	2	
217245_at	EPAG	early lymphoid activation protein	D	2	
220874_at	EPB41	erythrocyte membrane protein band 4.1 (elliptocytosis 1, RH-linked)	I	2	
210870_s_at	EPM2A	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin)	D	2	yes
239979_at	EPSTI1	epithelial stromal interaction 1 (breast)	I	2	

1570371_a_at	EPT1	ethanolaminephosphotransferase 1 (CDP-ethanolamine-specific)	D	2	
227016_at	ERICH1	glutamate-rich 1	I	2	
225764_at	ETV6	ets variant 6	I	2	yes
214285_at	FABP3	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)	I	2	
1557385_at	FAM161A	family with sequence similarity 161, member A	D	2	
229543_at	FAM26F	family with sequence similarity 26, member F	I	2	
216950_s_at	FCGR1A	Fc fragment of IgG, high affinity Ia, receptor (CD64)	I	2	yes
1554360_at; 231302_at	FCHSD2	FCH and double SH3 domains 2	I	2	
1553906_s_at	FGD2	FYVE, RhoGEF and PH domain containing 2	I	2	yes
224002_s_at	FKBP7	FK506 binding protein 7	D	2	
211454_x_at; 224288_x_at	FKSG49	FKSG49	I	2	
226419_s_at	FLJ44342	uncharacterized LOC645460	I	2	
228768_at	FNIP1	folliculin interacting protein 1	I	2	
1556667_at	FONG	uncharacterized LOC348751	D	2	
242938_s_at	FOXK2	forkhead box K2	D	2	
230645_at	FRMD3	FERM domain containing 3	I	2	
230744_at	FSTL1	follistatin-like 1	D	2	
1563509_at; 224148_at	FYB	FYN binding protein	I	2	
209416_s_at	FZR1	fizzy/cell division cycle 20 related 1 (Drosophila)	D	2	yes
202748_at; 242907_at	GBP2	guanylate binding protein 2, interferon-inducible	I	2	
229625_at	GBP5	guanylate binding protein 5	I	2	
211060_x_at	GPAA1	glycosylphosphatidylinositol anchor attachment protein 1 homolog (yeast)	D	2	
237690_at	GPR115	G protein-coupled receptor 115	I	2	
218468_s_at	GREM1	gremlin 1	I	2	yes
235957_at	GRIP1	glutamate receptor interacting protein 1	I	2	
213826_s_at	H3F3B	H3 histone, family 3B (H3.3B)	I	2	
205221_at	HGD	homogentisate 1,2-dioxygenase	I	2	
227614_at	HKDC1	hexokinase domain containing 1	D	2	
210747_at	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	I	2	yes
242001_at	IDH1	isocitrate dehydrogenase 1 (NADP+), soluble	I	2	
226757_at	IFIT2	interferon-induced protein with tetratricopeptide repeats 2	I	2	yes
229450_at	IFIT3	interferon-induced protein with tetratricopeptide repeats 3	I	2	
230128_at	IGLL5	immunoglobulin lambda-like polypeptide 5	I	2	
225025_at	IGSF8	immunoglobulin superfamily, member 8	D	2	
1562468_at	IL1RAP	interleukin 1 receptor accessory protein	I	2	yes
207688_s_at	INHBC	inhibin, beta C	I	2	yes
238725_at	IRF1	interferon regulatory factor 1	I	2	yes

210119_at; 216782_at	KCNJ15	potassium inwardly-rectifying channel, subfamily J, member 15	I	2	
231513_at; 206765_at	KCNJ2	potassium inwardly-rectifying channel, subfamily J, member 2	I	2	
1559023_a_at	KIAA0494	KIAA0494	I	2	
225193_at	KIAA1967	KIAA1967	D	2	yes
208784_s_at	KLHDC3	kelch domain containing 3	D	2	
1565690_at	KPNA3	karyopherin alpha 3 (importin alpha 4)	I	2	
208974_x_at	KPNB1	karyopherin (importin) beta 1	I	2	yes
1555384_a_at	LARP4	La ribonucleoprotein domain family, member 4	D	2	
215229_at	LOC100129973	uncharacterized LOC100129973	D	2	
1569746_s_at	LOC100505783	uncharacterized LOC100505783	I	2	
215322_at	LONRF1	LON peptidase N-terminal domain and ring finger 1	I	2	
233818_at	LTN1	listerin E3 ubiquitin protein ligase 1	I	2	
232283_at	LYSMD1	LysM, putative peptidoglycan-binding, domain containing 1	I	2	
215902_at	MARCH 6	membrane-associated ring finger (C3HC4) 6, E3 ubiquitin protein ligase	I	2	
1554730_at	MCTP1	multiple C2 domains, transmembrane 1	I	2	
235589_s_at	MDM4	Mdm4 p53 binding protein homolog (mouse)	I	2	yes
222567_s_at	MEX3C	mex-3 homolog C (C. elegans)	D	2	
241541_at	MIB2	mindbomb E3 ubiquitin protein ligase 2	I	2	
225826_at	MMAB	methylmalonic aciduria (cobalamin deficiency) cblB type	D	2	
239273_s_at	MMP28	matrix metallopeptidase 28	D	2	yes
221995_s_at	MRP63	mitochondrial ribosomal protein 63	I	2	
228846_at	MXD1	MAX dimerization protein 1	I	2	yes
211010_s_at	NCR3	natural cytotoxicity triggering receptor 3	D	2	yes
243357_at	NEGR1	neuronal growth regulator 1	D	2	
223218_s_at	NFKBIZ	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta	I	2	yes
214101_s_at	NPEPPS	aminopeptidase puromycin sensitive	I	2	
1557071_s_at	NUB1	negative regulator of ubiquitin-like proteins 1	I	2	yes
1561847_at	NUDT17	nudix (nucleoside diphosphate linked moiety X)-type motif 17	D	2	
1569990_at	NUDT3	nudix (nucleoside diphosphate linked moiety X)-type motif 3	I	2	
243934_at	ODF3B	outer dense fiber of sperm tails 3B	I	2	
229787_s_at	OGT	O-linked N-acetylglucosamine (GlcNAc) transferase	I	2	yes
1569617_at	OSBP2	oxysterol binding protein 2	D	2	
243287_s_at	OSTM1	osteopetrosis associated transmembrane protein 1	I	2	
231838_at	PABPC1L	poly(A) binding protein, cytoplasmic 1-like	I	2	
235157_at	PARP14	poly (ADP-ribose) polymerase family, member 14	I	2	
227807_at	PARP9	poly (ADP-ribose) polymerase family, member 9	I	2	
241956_at	PCGF5	polycomb group ring finger 5	I	2	

222045_s_at	PCIF1	PDX1 C-terminal inhibiting factor 1	D	2	
217695_x_at	PELI1	pellino E3 ubiquitin protein ligase 1	I	2	
225958_at	PHC1	polyhomeotic homolog 1 (Drosophila)	I	2	
237867_s_at	PID1	phosphotyrosine interaction domain containing 1	D	2	
216112_at	PKN2	protein kinase N2	I	2	yes
241916_at	PLSCR1	phospholipid scramblase 1	I	2	yes
235508_at	PML	promyelocytic leukemia	I	2	yes
202884_s_at	PPP2R1B	protein phosphatase 2, regulatory subunit A, beta	D	2	yes
1559119_at	PPP6R3	protein phosphatase 6, regulatory subunit 3	I	2	
221270_s_at	QTRT1	queuine tRNA-ribosyltransferase 1	D	2	
241320_at	R3HDM1	R3H domain containing 1	I	2	
1553285_s_at	RAD9B	RAD9 homolog B (S. pombe)	I	2	
202052_s_at	RAI14	retinoic acid induced 14	D	2	yes
230466_s_at	RASSF3	Ras association (RalGDS/AF-6) domain family member 3	I	2	
204927_at	RASSF7	Ras association (RalGDS/AF-6) domain family (N-terminal) member 7	D	2	
237626_at	RB1CC1	RB1-inducible coiled-coil 1	I	2	yes
232150_at	RBCK1	RanBP-type and C3HC4-type zinc finger containing 1	I	2	yes
1560340_s_at	RP9P	retinitis pigmentosa 9 pseudogene	I	2	
214041_x_at	RPL37A	ribosomal protein L37a	I	2	
200908_s_at	RPLP2	ribosomal protein, large, P2	I	2	
242625_at	RSAD2	radical S-adenosyl methionine domain containing 2	I	2	
214370_at	S100A8	S100 calcium binding protein A8	I	2	yes
242190_at	SDAD1	SDA1 domain containing 1	I	2	
214257_s_at	SEC22B	SEC22 vesicle trafficking protein homolog B (S. cerevisiae) (gene/pseudogene)	I	2	
223121_s_at	SFRP2	secreted frizzled-related protein 2	D	2	yes
35626_at	SGSH	N-sulfoglucosamine sulfohydrolase	D	2	
228527_s_at	SLC25A37	solute carrier family 25 (mitochondrial iron transporter), member 37	I	2	
234268_at	SLC2A13	solute carrier family 2 (facilitated glucose transporter), member 13	I	2	
235536_at	SNORD89	small nucleolar RNA, C/D box 89	I	2	
208012_x_at; 209762_x_at	SP110	SP110 nuclear body protein	I	2	
228975_at	SP6	Sp6 transcription factor	D	2	
1557593_at	SPAG17	sperm associated antigen 17	D	2	
202523_s_at	SPOCK2	sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 2	D	2	
243522_at	SPPL3	signal peptide peptidase like 3	I	2	
213562_s_at	SQLE	squalene epoxidase	D	2	
219055_at	SRBD1	S1 RNA binding domain 1	I	2	
1565566_a_at	STX7	syntaxin 7	I	2	
1557305_at	TACC1	transforming, acidic coiled-coil containing protein 1	I	2	

216226_at	TAF4B	TAF4b RNA polymerase II, TATA box binding protein (TBP)-associated factor, 105kDa	D	2	
231193_s_at	TAOK1	TAO kinase 1	I	2	yes
225973_at	TAP2	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	I	2	
221398_at	TAS2R8	taste receptor, type 2, member 8	I	2	
213401_s_at	TBL1X	transducin (beta)-like 1X-linked	I	2	
1566208_at	TCEA1	transcription elongation factor A (SII), 1	I	2	
1552804_a_at	TIRAP	toll-interleukin 1 receptor (TIR) domain containing adaptor protein	D	2	yes
224321_at	TMEFF2	transmembrane protein with EGF-like and two follistatin-like domains 2	I	2	
235159_at 243465_at	TMEM140	transmembrane protein 140	I	2	
238063_at	TMEM154	transmembrane protein 154	I	2	
227386_s_at	TMEM200B	transmembrane protein 200B	I	2	
1554206_at	TMLHE	trimethyllysine hydroxylase, epsilon	I	2	
206025_s_at; 206026_s_at	TNFAIP6	tumor necrosis factor, alpha-induced protein 6	I	2	
1555557_a_at	TNK2	tyrosine kinase, non-receptor, 2	D	2	
1558354_s_at	TOP1	topoisomerase (DNA) I	I	2	yes
231978_at	TPCN2	two pore segment channel 2	I	2	
223599_at	TRIM6	tripartite motif containing 6	I	2	
242688_at	TRIP12	thyroid hormone receptor interactor 12	I	2	
1565887_at	TRPM7	transient receptor potential cation channel, subfamily M, member 7	I	2	yes
215107_s_at	TTC22	tetratricopeptide repeat domain 22	D	2	
202476_s_at	TUBGCP2	tubulin, gamma complex associated protein 2	D	2	yes
228588_s_at	UBE2B	ubiquitin-conjugating enzyme E2B	I	2	yes
1568903_at	UBR5	ubiquitin protein ligase E3 component n-recognin 5	I	2	yes
205586_x_at	VGF	VGF nerve growth factor inducible	D	2	
242390_at	WDFY1	WD repeat and FYVE domain containing 1	I	2	
201421_s_at	WDR77	WD repeat domain 77	D	2	
1569428_at	WIBG	within bgcn homolog (Drosophila)	D	2	yes
213734_at	WSB2	WD repeat and SOCS box containing 2	I	2	
228617_at	XAF1	XIAP associated factor 1	I	2	yes
1554037_a_at	ZBTB24	zinc finger and BTB domain containing 24	D	2	
219062_s_at	ZCCHC2	zinc finger, CCHC domain containing 2	I	2	
1555982_at	ZFYVE16	zinc finger, FYVE domain containing 16	I	2	
228864_at	ZNF653	zinc finger protein 653	D	2	

Table S4. Extended Biological Pathways Analyses

A.	INGENUITY Pathways				KEGG Pathways		
	#	Top Canonical Pathways	P-Value	Ratio	Pathway Name	Enrichment Score	Enrichment p-value
Genes with CFG score>=6.0 N=21 genes	1	Role of Tissue Factor in Cancer	2.63E-04	3/115 (0.026)	**Apoptosis**	6.69102	0.001242
	2	Dendritic Cell Maturation	9.83E-04	3/207 (0.014)	Measles	6.06369	0.002326
	3	Melanoma Signaling	1.13E-03	2/46 (0.043)	Endometrial cancer	4.96787	0.006958
	4	**Docosahexaenoic Acid (DHA) Signaling**	1.18E-03	2/49 (0.041)	Influenza A	4.90223	0.00743
	5	Endometrial Cancer Signaling	1.69E-03	2/57 (0.035)	Phosphatidylinositol signaling system	4.85448	0.007793
	#	**Top Canonical Pathways**	P-Value	Ratio	**Pathway Name**	Enrichment Score	Enrichment p-value
Genes with CFG score>=4.0 N=41 genes	1	NF-kB Signaling	4.42E-04	4/175 (0.023)	Measles	8.7667	0.000156
	2	Dendritic Cell Maturation	5.38E-04	4/207 (0.019)	Influenza A	6.87308	0.001035
	3	PDGF Signaling	7.50E-04	3/85 (0.035)	mTOR signaling pathway	6.34986	0.001747
	4	Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	1.14E-03	3/106 (0.028)	**Apoptosis**	4.75687	0.008592
	5	Role of Tissue Factor in Cancer	1.78E-03	3/115 (0.026)	Toll-like receptor signaling pathway	4.37269	0.012617
	#	**Top Canonical Pathways**	P-Value	Ratio	**Pathway Name**	Enrichment Score	Enrichment p-value
All genes differentially expressed (Table S2) N=246 genes (279 probesets)	1	**Retinoic acid Mediated Apoptosis Signaling**	1.12E-03	5/69 (0.072)	Ubiquitin mediated proteolysis	4.80416	0.0081956
	2	Role of PKR in Interferon Induction and Antiviral Response	1.19E-03	4/46 (0.087)	Herpes simplex infection	4.14288	0.0158771
	3	UVA-Induced MAPK Signaling	3.90E-03	5/92 (0.054)	Phagosome	4.0301	0.0177725
	4	Dendritic Cell Maturation	4.71E-03	7/207 (0.034)	Measles	3.72158	0.0241958
	5	Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	5.38E-03	5/106 (0.047)	Influenza A	5.03358	0.0065155

Table S5. Ingenuity drug targets analysis. Repositioning of existing drugs to be potentially tested for treating suicidality.

	CFG Score	Direction of change	Location	Type(s)	Drug(s)
IL1B interleukin 1, beta	8	I	Extracellular Space	cytokine	IL-1 trap, canakinumab
KCNJ2 potassium inwardly-rectifying channel, subfamily J, member 2	4	I	Plasma Membrane	ion channel	nicorandil, amiodarone
PML promyelocytic leukemia	4	I	Nucleus	transcription regulator	arsenic trioxide
TNK2 tyrosine kinase, non-receptor, 2	4	D	Cytoplasm	kinase	vemurafenib
TOP1 topoisomerase (DNA) I	2	I	Nucleus	enzyme	elsamitrucin,T 0128,CT-2106,BN 80927,tafluposide,TAS-103,beta-lapachone,irinotecan,topotecan,9-amino-20-camptothecin,rubitecan,gimatecan,karenitecin

Table S6. Genes in our dataset modulated by Clozapine and Omega-3 Fatty Acids (DHA). Bold are genes that are changed in opposite direction to SI by one or both of the treatments.

Gene Symbol	Gene Name	Direction of Change	CFG score	Modulated by Clozapine[1, 2]	Modulated by DHA[3]
SAT1	**spermidine/spermine N1-acetyl transferase 1**	**I**	**8**		**(D) Blood**
GBP1	**guanylate nucleotide binding protein 1**	**I**	**8**		**(D) Blood**
ATP13A2	ATPase type 13A2	D	6	(D) VT	
EPHX1	epoxide hydrolase 1, microsomal	D	6	(D) VT	
IL1B	**interleukin 1 beta**	**I**	**6**	(I) Blood	**(D) Blood**
LHFP	**lipoma HMGIC fusion partner**	**I**	**6**	(I) Blood, VT	**(D) Blood**
MARCKS	myristoylated alanine rich protein kinase C substrate	I	6		(I) HIP
PTEN	phosphatase and tensin homolog	I	6	(I) VT	
SPTBN1	**spectrin, beta, non-erythrocytic 1**	**D**	**6**	**(I) Blood, VT**	(D) Blood
ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	I	4	(I) VT	
MAP3K3	**mitogen-activated protein kinase kinase kinase 3**	**I**	**4**		**(D) Blood**
MBNL2	**muscleblind-like 2**	**D**	**4**	**(I) Blood**	(D) Blood
ATG3	**autophagy-related 3 (yeast)**	**I**	**2**		**(D) Blood**
ATXN2	ataxin 2	I	2	(I) VT	
CCR1	**chemokine (C-C motif) receptor 1**	**I**	**2**		**(D) Blood**
CCRN4L	CCR4 carbon catabolite repression 4-like	I	2		(I) Blood
CD84	**CD84 antigen**	**D**	**2**	**(I) Blood**	(D) Blood
CEACAM1	**CEA-related cell adhesion molecule 1**	**I**	**2**		**(D) Blood**
CELA1	chymotrypsin-like elastase family, member 1	D	2		(D) Blood
CLEC4E	**C-type lectin domain family 4, member e**	**I**	**2**		**(D) Blood**
CLEC7A	**C-type lectin domain family 7, member a**	**I**	**2**		**(D) Blood**
CORO1C	coronin, actin binding protein 1C	I	2	(D) VT	
DLGAP1	discs, large (Drosophila) homolog-associated protein 1	I	2	(I) VT	

DOCK1	dedicator of cytokinesis 1	D	2	(D) VT	
DOCK4	dedicator of cytokinesis 4	I	2	(D) HIP	
FABP3	fatty acid binding protein 3, muscle and heart	I	2	(I) VT	
FNIP1	folliculin interacting protein 1	I	2	(I) VT	
FOXK2	forkhead box K2	D	2	(I) VT	
FZR1	**fizzy/cell division cycle 20 related 1 (Drosophila)**	**D**	**2**		**(I) Blood**
GBP2	guanylate nucleotide binding protein 2	I	2	(D) VT	
GREM1	gremlin 1	I	2		(D) HIP
IFIT2	**interferon-induced protein with tetratricopeptide repeats 2**	**I**	**2**	(I) Blood	**(D) Blood**
IFIT3	interferon-induced protein with tetratricopeptide repeats 3	I	2		(D) NAC
IL1RAP	interleukin 1 receptor accessory protein	I	2	(I) VT	
KLHDC3	kelch domain containing 3	D	2	(I) VT	
KPNA3	karyopherin (importin) alpha 3	I	2	(D) VT	
LARP4	La ribonucleoprotein domain family, member 4	D	2	(I) VT	
LONRF1	LON peptidase N-terminal domain and ring finger 1	I	2	(I) VT	
MCTP1	multiple C2 domains, transmembrane 1	I	2		(I) HIP
MDM4	**transformed mouse 3T3 cell double minute 4**	**I**	**2**		**(D) Blood**
NUB1	negative regulator of ubiquitin-like proteins 1	I	2	(D) VT	
NUDT3	**nudix (nucleotide diphosphate linked moiety X)-type motif 3**	**I**	**2**		**(D) Blood**
OGT	O-linked N-acetylglucosamine (GlcNAc) transferase	I	2	(I) Blood	(D) HIP; (I) NAC
PELI1	pellino 1	I	2	(I) AMY	(I) HIP
PKN2	protein kinase N2	I	2		(I) Blood
R3HDM1	**R3H domain 1 (binds single-stranded nucleic acids)**	**I**	**2**	**(I) VT**	**(D) Blood**
RAI14	retinoic acid induced 14	D	2		(I) HIP
RASSF3	**Ras association (RalGDS/AF-6) domain family member 3**	**I**	**2**	**(I) VT**	**(D) Blood**

RPL37A	ribosomal protein L37a	I	2		(I) Blood
RPLP2	ribosomal protein, large P2	I	2		(I) Blood
RSAD2	radical S-adenosyl methionine domain containing 2	I	2	(I) Blood	(I) Blood
S100A8	**S100 calcium binding protein A8 (calgranulin A)**	**I**	**2**	**(D) Blood**	**(D) Blood**
SFRP2	secreted frizzled-related protein 2	D	2	(D) VT	
SLC25A37	solute carrier family 25, member 37	I	2	(I) VT	(I) Blood
SLC2A13	solute carrier family 2 (facilitated glucose transporter), member 13	I	2	(I) VT	
SPOCK2	sparc/osteonectin, cwcv and kazal-like domains proteoglycan 2	D	2	(I) VT	
TAOK1	TAO kinase 1	I	2	(I) VT	(D) PFC; (I) HIP
TB1X	transducin (beta)-like 1 X-linked	I	2	(D) VT	
TCEA1	transcription elongation factor A (SII) 1	I	2	(D) VT	(I) Blood
TMEM140	**transmembrane protein 140**	**I**	**2**	**(I) Blood**	**(D) Blood**
TMEM154	**transmembrane protein 154**	**I**	**2**		**(D) Blood**
TNFAIP6	tumor necrosis factor alpha induced protein 6	I	2	(I) AMY	
TNK2	tyrosine kinase, non-receptor, 2	D	2	(D) VT	
TOP1	topoisomerase (DNA) I	I	2	(I) VT	(I) Blood
TRIP12	thyroid hormone receptor interactor 12	I	2	(I) VT	
TRPM7	transient receptor potential cation channel, subfamily M, member 7	I	2		(D) AMY
UBE2B	ubiquitin-conjugating enzyme E2B, RAD6 homology (S. cerevisiae)	I	2	(I) Blood, AMY, PFC	(I) Blood
WDR77	WD repeat domain 77	D	2	(D) VT	

Table S7. Genes in our dataset with evidence as mood and/or psychosis blood biomarkers.

Gene Symbol	Gene Name	CFG score in SI	Direction of change in SI	Direction of change in Mood [4]	Direction of change in Hallucinations[2]	Direction of change in Delusions[2]
LEPR	leptin receptor	6	D	(I)		
CD84	CD84 molecule	2	D			(I)
DOCK5	dedicator of cytokinesis 5	2	I	(D)	(I)	
EPM2A	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin)	2	D			(D)
ERICH1	glutamate-rich 1	2	I		(D)	(D)
FKBP7	FK506 binding protein 7	2	D			(D)
IDH1	isocitrate dehydrogenase 1 (NADP+), soluble	2	I			(D)
KIAA0494	KIAA0494	2	I	(D)		
LARP4	La ribonucleoprotein domain family, member 4	2	D	(D)		
MXD1	MAX dimerization protein 1	2	I			(I)
PID1	phosphotyrosine interaction domain containing 1	2	D			(D)
PML	promyelocytic leukemia	2	I			(I)
PPP2R1B	protein phosphatase 2, regulatory subunit A, beta	2	D			(D)
SLC2A13	solute carrier family 2 (facilitated glucose transporter), member 13	2	I	(D)		
TRIM6	tripartite motif containing 6	2	I	(D)		
TRPM7	transient receptor potential cation channel, subfamily M, member 7	2	I	(I)		

Table S8. Biomarkers for suicidality in our dataset with postmortem brain gene expression evidence in other psychiatric disorders. From among the top validated biomarkers from Figure 3C.

Biomarker For Suicidality	Other Psychiatric Disorders Postmortem Brain Gene Expression Evidence
SAT1	Depression (Gaiteri et al. 2010) [5]
MARCKS	Schizophrenia (Hakak et al. 2001)[6] Depression (Pandey et al. 2003)[7]
PTEN	Schizophrenia (Miller et al. 2012)[8] Depression (Karege et al. 2011)[9]
FOXN3	Schizophrenia (Mudge et al. 2008)[10] Depression (Gaiteri et al. 2010) [5]

Table S9. Demographic data for live psychosis follow-up cohort (n=46).

A. Individual. B. Aggregate.

A

SubjectID-Visit	Diagnosis	Age	Gender	Ethnicity	SAT1 Levels	Years since testing	Future Hosp. w/o suicidality	Future Hosp. due to suicidality	Frequency of Future Hosp. w/o suicidality	Frequency of Future Hosp. due to suicidality
phchp222v2	Schizophrenia	60	M	Caucasian	1410.6	0.67	0	0	0	0
phchp175v1	Schizoaffective Disorder	42	M	Caucasian	1773.9	2.08	0	0	0	0
phchp139v1	Schizophrenia	24	M	Caucasian	1774.6	0.25	0	0	0	0
phchp025v1	Schizophrenia	42	M	Caucasian	2004.6	6.83	0	0	0	0
phchp051v1	Schizoaffective Disorder	52	M	Caucasian	2083.8	5.83	0	0	0	0
phchp148v1	Schizophrenia	25	M	Caucasian	2254.7	2.17	1	0	0.46	0
phchp133v1	Schizophrenia	55	M	Caucasian	2286	2.75	0	2	0	0.73
phchp033v1	Schizoaffective Disorder	48	M	Caucasian	2291.4	2.58	0	1	0	0.39
phchp027v1	Schizoaffective Disorder	40	M	Caucasian	2406.3	6.67	3	0	0.45	0
phchp012v1	Schizoaffective Disorder	55	M	Caucasian	2458.1	5.17	1	1	0.19	0.19
phchp089v2	Schizoaffective Disorder	33	M	Caucasian	2545.3	4.42	0	0	0	0
phchp060v1	Schizophrenia	62	M	Caucasian	2589.2	3.50	2	0	0.57	0
phchp046v1	Schizoaffective Disorder	45	M	Caucasian	2732.3	6.17	0	1	0	0.16
phchp103v1	Schizoaffective Disorder	61	M	Caucasian	2763.7	2.58	1	2	0.39	0.77
phchp010v2	Schizoaffective Disorder	45	M	Caucasian	2778.5	6.92	0	0	0	0
phchp005v1	Schizoaffective Disorder	45	M	Caucasian	2797.8	7.33	1	1	0.14	0.14
phchp022v1	Schizophrenia	48	M	Caucasian	2846.6	6.83	0	0	0	0
phchp195v3	Schizophrenia	53	M	Caucasian	2846.6	1.17	0	0	0	0
phchp129v1	Schizoaffective Disorder	22	M	Caucasian	2871.5	2.83	5	1	1.76	0.35
phchp120v1	Delusional Disorder	51	M	Caucasian	2877.9	3.00	0	0	0	0
phchp211v1	Schizophrenia	62	M	Caucasian	2879.9	1.25	0	0	0	0
phchp277v2	Schizophrenia	50	M	Caucasian	2904.8	0.58	0	0	0	0
phchp101v1	Schizoaffective Disorder	74	M	Caucasian	2923.7	3.67	0	1	0	0.27
phchp116v1	Schizoaffective Disorder	47	M	Caucasian	2962.1	0.50	0	1	0	2.00
phchp052v1	Schizophrenia	60	M	Caucasian	2989.9	0.83	0	0	0	0
phchp090v3	Schizophrenia	24	M	Caucasian	3046.4	1.00	0	2	0	2.00

phchp197v1	Schizophrenia	56	M	Caucasian	3046.6	1.67	1	0	0.60	0
phchp061v3	Schizophrenia	50	M	Caucasian	3115.6	4.92	1	6	0.20	1.22
phchp057v1	Schizoaffective Disorder	47	M	Caucasian	3233.8	5.92	0	0	0	0
phchp105v1	Schizoaffective Disorder per chip	59	M	Caucasian	3297.6	2.83	2	0	0.71	0
phchp087v3	Schizoaffective Disorder	66	M	Caucasian	3523.5	4.25	0	0	0	0
phchp091v1	Schizoaffective Disorder	55	M	Caucasian	3534.5	4.75	0	0	0	0
phchp069v3	Schizophrenia	48	M	Caucasian	3819.8	5.25	0	0	0	0
phchp062v3	Schizophrenia	57	M	Caucasian	3878.8	5.42	0	0	0	0
phchp099v2	Schizophrenia	49	M	Caucasian	3993.4	3.58	0	0	0	0
phchp049v1	Schizoaffective Disorder	46	M	Caucasian	4012.3	6.08	0	0	0	0
phchp040v3	Schizoaffective Disorder	50	M	Caucasian	4019.2	5.25	1	0	0.19	0
phchp042v3	Schizoaffective Disorder	44	M	Caucasian	4124.5	5.50	0	0	0	0
phchp075v3	Schizoaffective Disorder	58	M	Caucasian	4127.1	4.83	1	5	0.21	1.03
phchp108v2	Schizophrenia	42	M	Caucasian	4231.9	3.17	0	0	0	0
phchp085v3	Schizoaffective Disorder	57	M	Caucasian	4335.9	4.50	0	0	0	0
phchp151v3	Schizophrenia	24	M	Caucasian	4390.9	2.00	1	1	0.50	0.50
phchp065v3	Schizoaffective Disorder	62	M	Caucasian	4439.2	5.25	0	0	0	0
phchp086v3	Schizophrenia	49	M	Caucasian	4545.4	4.25	0	0	0	0
phchp073v3	Schizoaffective Disorder	65	M	Caucasian	4874.4	4.92	0	12	0	2.44
phchp072v3	Schizoaffective Disorder	60	M	Caucasian	5911.1	5.08	0	1	0	0.20

B

SAT1 levels	***Lower Tertile***	***Upper Tertile***
Number of subjects	15	15
Age mean year (SD) range	45.4 (11.4) 36-64	51.1 (10.1) 28-61
Diagnosis (Schizophrenia/ Schizoaffective)	(8/7)	(6/9)

Table S10. Past Hospitalizations

A. Bipolar

SubjectID-Visit	Diagnosis	Age	Gender	Ethnicity	SAT1 Levels at testing	Years follow-up prior to testing	Past Hosp. w/o suicidality	Past Hosp. due to suicidality	Frequency of Past Hosp. w/o suicidality	Frequency of Past Hosp. due to suicidality
phchp234v1	Bipolar II Disorder	44	M	Caucasian	1955.2	0.916667	0	0	0	0
phchp053v2	Bipolar I Disorder	58	M	Caucasian	2178.3	10.41667	8	1	0.77	0.10
phchp152v1	Bipolar I Disorder	45	M	Caucasian	2178.8	12.58333	7	0	0.56	0
phchp122v1	Bipolar Disorder NOS	51	M	Caucasian	2245.6	5.333333	0	0	0	0
phchp190v3	Bipolar Disorder NOS	50	M	Caucasian	2300.6	5.25	0	0	0	0
phchp020v3	Bipolar Disorder NOS	63	M	Caucasian	2342.6	8.5	0	0	0	0
phchp113v1	Bipolar I Disorder	37	M	Caucasian	2437.4	2	0	0	0	0
phchp132v2	Bipolar I Disorder	51	M	Caucasian	2558.9	7	2	0	0.29	0
phchp184v3	Bipolar Disorder NOS	64	M	Caucasian	2575.4	16.75	0	0	0	0
phchp039v3	Bipolar I Disorder	52	M	Caucasian	2580.1	7.166667	2	0	0.28	0
phchp147v1	Bipolar II Disorder	38	M	Caucasian	2582.8	7	0	0	0	0
phchp178v1	Bipolar I Disorder	49	M	Caucasian	2616.8	14.41667	1	5	0.07	0.35
phchp136v3	Bipolar I Disorder	41	M	Caucasian	2635.9	4.666667	3	0	0.64	0
phchp045v3	Bipolar I Disorder	36	M	Caucasian	2721	4.666667	0	0	0	0
phchp224v1	Bipolar I Disorder	59	M	Caucasian	2748.1	1.416667	1	0	0.71	0
phchp183v1	Bipolar I Disorder	48	M	Caucasian	2750.9	1.75	1	1	0.57	0.57
phchp171v2	Bipolar Disorder NOS	36	M	Caucasian	2795.7	2.25	0	0	0	0
phchp166v1	Bipolar Disorder NOS	56	M	Caucasian	2829.6	0.833333	0	2	0	2.40
phchp253v1	Bipolar Disorder NOS	25	M	Caucasian	2888.5	0.25	0	0	0	0
phchp186v1	Bipolar II Disorder	43	M	Caucasian	2901.5	6.75	0	0	0	0
phchp079v2	Bipolar Disorder	44	M	Caucasian	3053.2	3.083333	0	0	0	0
phchp128v1	Bipolar I Disorder	45	M	Caucasian	3118.6	19.66667	2	0	0.10	0
phchp080v1	Bipolar I Disorder	44	M	Caucasian	3153.6	10.5	0	0	0	0
phchp088v1	Bipolar I Disorder	44	M	Caucasian	3194.1	2.416667	0	1	0	0.41
phchp109v1	Bipolar I Disorder	22	M	Caucasian	3200.8	0	0	0	0	0
phchp134v3	Bipolar II Disorder	59	M	Caucasian	3202.3	15.75	1	0	0.06	0

phchp153v1	Bipolar II Disorder	55	M	Caucasian	3304.9	0.25	0	2	0	8.00
phchp274v2	Bipolar Disorder NOS	48	M	Caucasian	3349	11	0	4	0	0.36
phchp140v3	Bipolar II Disorder	38	M	Caucasian	3393.8	9	0	0	0	0
phchp030v3	Bipolar I Disorder	49	M	Caucasian	3395.2	1.666667	0	4	0	2.40
phchp124v1	Bipolar I Disorder	53	M	Caucasian	3660.9	8.916667	2	3	0.22	0.34
phchp095v3	Bipolar I Disorder	29	M	Caucasian	3695.4	0.916667	0	3	0	3.27
phchp100v1	Bipolar I Disorder	28	M	Caucasian	3767.8	3.333333	0	4	0	1.20
phchp210v3	Bipolar I Disorder	44	M	Caucasian	3844.6	10.75	0	0	0	0
phchp219v1	Bipolar Disorder NOS	61	M	Caucasian	3845.1	11.08333	0	1	0	0.09
phchp031v3	Bipolar I Disorder	52	M	Caucasian	4080.7	0.583333	4	0	6.86	0
phchp093v3	Bipolar I Disorder	52	M	Caucasian	4137.4	2.333333	0	1	0	0.43
phchp067v1	Bipolar II Disorder	39	M	Caucasian	4214.7	3.75	0	0	0	0
phchp142v3	Bipolar I Disorder	55	M	Caucasian	4310.7	1.333333	0	0	0	0
phchp112v2	Bipolar I Disorder	46	M	Caucasian	4410.4	0.333333	1	0	3.00	0
phchp149v2	Bipolar Disorder NOS	45	M	Caucasian	4586.9	0.583333	1	0	1.71	0
phchp117v1	Bipolar I Disorder	43	M	Caucasian	6531.1	5.25	0	0	0	0

B. Psychosis

SubjectID-Visit	Diagnosis	Age	Gender	Ethnicity	SAT1 Levels	Years follow-up prior to testing	Past Hosp. w/o suicidality	Past Hosp. due to suicidality	Frequency of Past Hosp. w/o suicidality	Frequency of Past Hosp. due to suicidality
phchp222v2	Schizophrenia	60	M	Caucasian	1410.6	18	0	0	0	0
phchp175v1	Schizoaffective Disorder	42	M	Caucasian	1773.9	0.5	1	0	2	0
phchp139v1	Schizophrenia	24	M	Caucasian	1774.6	0	0	0	0	0
phchp025v1	Schizophrenia	42	M	Caucasian	2004.6	11.42	2	0	0.18	0
phchp051v1	Schizoaffective Disorder	52	M	Caucasian	2083.8	9.25	3	0	0.32	0
phchp148v1	Schizophrenia	25	M	Caucasian	2254.7	0.5	0	0	0	0
phchp133v1	Schizophrenia	55	M	Caucasian	2286	12.25	0	2	0	0.16
phchp033v1	Schizoaffective Disorder	48	M	Caucasian	2291.4	0	0	0	0	0
phchp027v1	Schizoaffective Disorder	40	M	Caucasian	2406.3	11.42	3	3	0.26	0.26
phchp012v1	Schizoaffective Disorder	55	M	Caucasian	2458.1	14.42	2	0	0.14	0
phchp089v2	Schizoaffective Disorder	33	M	Caucasian	2545.3	4.67	0	1	0	0.21

phchp060v1	Schizophrenia	62	M	Caucasian	2589.2	12.5	13	5	1.04	0.4
phchp046v1	Schizoaffective Disorder	45	M	Caucasian	2732.3	11.83	0	2	0	0.17
phchp103v1	Schizoaffective Disorder	61	M	Caucasian	2763.7	14.92	3	1	0.20	0.07
phchp010v2	Schizoaffective Disorder	45	M	Caucasian	2778.5	10.67	2	0	0.19	0
phchp005v1	Schizoaffective Disorder	45	M	Caucasian	2797.8	9.67	1	1	0.10	0.10
phchp022v1	Schizophrenia	48	M	Caucasian	2846.6	11.33	0	0	0	0
phchp195v3	Schizophrenia	53	M	Caucasian	2846.6	4.83	0	0	0	0
phchp129v1	Schizoaffective Disorder	22	M	Caucasian	2871.5	1.42	0	0	0	0
phchp120v1	Delusional Disorder	51	M	Caucasian	2877.9	8.75	0	0	0	0
phchp211v1	Schizophrenia	62	M	Caucasian	2879.9	15.83	1	0	0.06	0
phchp277v2	Schizophrenia	50	M	Caucasian	2904.8	16.67	1	0	0.06	0
phchp101v1	Schizoaffective Disorder	74	M	Caucasian	2923.7	10.5	0	1	0	0.10
phchp116v1	Schizoaffective Disorder	47	M	Caucasian	2962.1	1.83	1	0	0.55	0
phchp052v1	Schizophrenia	60	M	Caucasian	2989.9	17.42	7	0	0.40	0
phchp090v3	Schizophrenia	24	M	Caucasian	3046.4	0.5	0	1	0	2.00
phchp197v1	Schizophrenia	56	M	Caucasian	3046.6	12.92	1	1	0.08	0.08
phchp061v3	Schizophrenia	50	M	Caucasian	3115.6	3.83	7	6	1.83	1.57
phchp057v1	Schizoaffective Disorder	47	M	Caucasian	3233.8	4.92	1	0	0.20	0
phchp105v1	Schizoaffective Disorder per chip	59	M	Caucasian	3297.6	9	2	0	0.22	0
phchp087v3	Schizoaffective Disorder	66	M	Caucasian	3523.5	12.75	6	1	0.47	0.08
phchp091v1	Schizoaffective Disorder	55	M	Caucasian	3534.5	2.25	0	0	0	0
phchp069v3	Schizophrenia	48	M	Caucasian	3819.8	14.25	3	5	0.21	0.35
phchp062v3	Schizophrenia	57	M	Caucasian	3878.8	10	0	0	0	0
phchp099v2	Schizophrenia	49	M	Caucasian	3993.4	12.08	0	0	0	0
phchp049v1	Schizoaffective Disorder	46	M	Caucasian	4012.3	5.67	0	1	0	0.18
phchp040v3	Schizoaffective Disorder	50	M	Caucasian	4019.2	15.75	1	0	0.06	0
phchp042v3	Schizoaffective Disorder	44	M	Caucasian	4124.5	1	0	1	0	1.00
phchp075v3	Schizoaffective Disorder	58	M	Caucasian	4127.1	10.08	1	4	0.10	0.40
phchp108v2	Schizophrenia	42	M	Caucasian	4231.9	17.25	2	0	0.12	0
phchp085v3	Schizoaffective Disorder	57	M	Caucasian	4335.9	13.25	1	0	0.08	0
phchp151v3	Schizophrenia	24	M	Caucasian	4390.9	0.92	0	5	0	5.45
phchp065v3	Schizoaffective Disorder	62	M	Caucasian	4439.2	7.92	0	0	0	0
phchp086v3	Schizophrenia	49	M	Caucasian	4545.4	9.33	0	0	0	0
phchp073v3	Schizoaffective Disorder	65	M	Caucasian	4874.4	5.33	3	13	0.56	2.44
phchp072v3	Schizoaffective Disorder	60	M	Caucasian	5911.1	4.33	0	0	0	0

Table S11. Prospective and retrospective differentiation of hospitalizations with suicidality. The top 6 biomarkers for suicidality from the live bipolar discovery cohort, that subsequently survived filtering through the postmortem coroner's office cohort and Bonferroni correction (as in Figure 3) were then tested in two other live cohorts, one bipolar and one psychosis (as in Figure 6 and Figures S2, S3 and S4). SAT1 shows the strongest individual results, prospective and retrospective. A panel of 3 biomarkers, and a panel of the 6 biomarkers, showed even stronger results than the individual biomarkers. For panels, Z-scored expression data from the individual biomarkers was used in an additive fashion to generate a score. H- upper half vs. lower half biomarker scores. T- upper tertile vs. lower tertile biomarker scores. P-values from one-tail t-test with equal variance are depicted in the table. **Bold- significant results.** ***Italics- trend.*** NS-non-significant.

	Bipolar Disorder (n=42)				Psychosis (n=46) Schizophrenia/Schizoaffective			
	Future Hospitalizations (since testing)		Past Hospitalizations (prior to testing)		Future Hospitalizations (since testing)		Past Hospitalizations (prior to testing)	
	Without	**With Suicidality**	Without	**With Suicidality**	Without	**With Suicidality**	Without	**With Suicidality**
SAT1	NS	H:0.1195 **T: 0.0484**	NS	H:0.0743 **T: 0.0363**	NS	NS ***(H:0.0519***)	NS	**H: 0.0274** T:0.0742
PTEN	NS	**H:0.0271** **T: 0.0324**	NS	H:0.0598 **T: 0.0491**	NS	NS	NS	NS
MARCKS	NS	NS	NS	**H: 0.0227** **T: 0.0242**	NS	NS	NS	NS
MAP3K3	NS	NS	NS	H:0.2052 **T: 0.0273**	NS	NS	NS	NS
UBA6	NS	NS	NS	NS	NS	NS	NS	NS
MT-ND6	NS	NS	NS	NS	NS	NS	NS	NS
Panel of 3 (SAT1, PTEN, MAP3K3)	NS	**H:0.0184** T:0.0530	NS	**H:0.04905** **T:0.04914**	NS	NS	NS	NS
Panel of 6 (SAT1, PTEN, MAP3K3, UBA6, MARCK6, MT-ND6)	NS	H:0.1501 **T: 0.0159**	NS	H:0.0728 **T: 0.0101**	NS	NS	NS	NS

Table S12. SAT1 Expression Levels Cut-offs from the ROC Curve (Figure 6)

Cut-off	SAT1 expression levels	Sensitivity	Specificity	Accuracy
Higher Sensitivity	2734.512	100.00%	41.18%	70.59%
Intermediate	3173.874	75.00%	61.76%	68.38%
Higher Specificity	3394.539	50.00%	73.53%	61.77%

Figure S1. Scatter plot of data from the testing of SAT1 and CD24 in suicide completers (Figure 6)

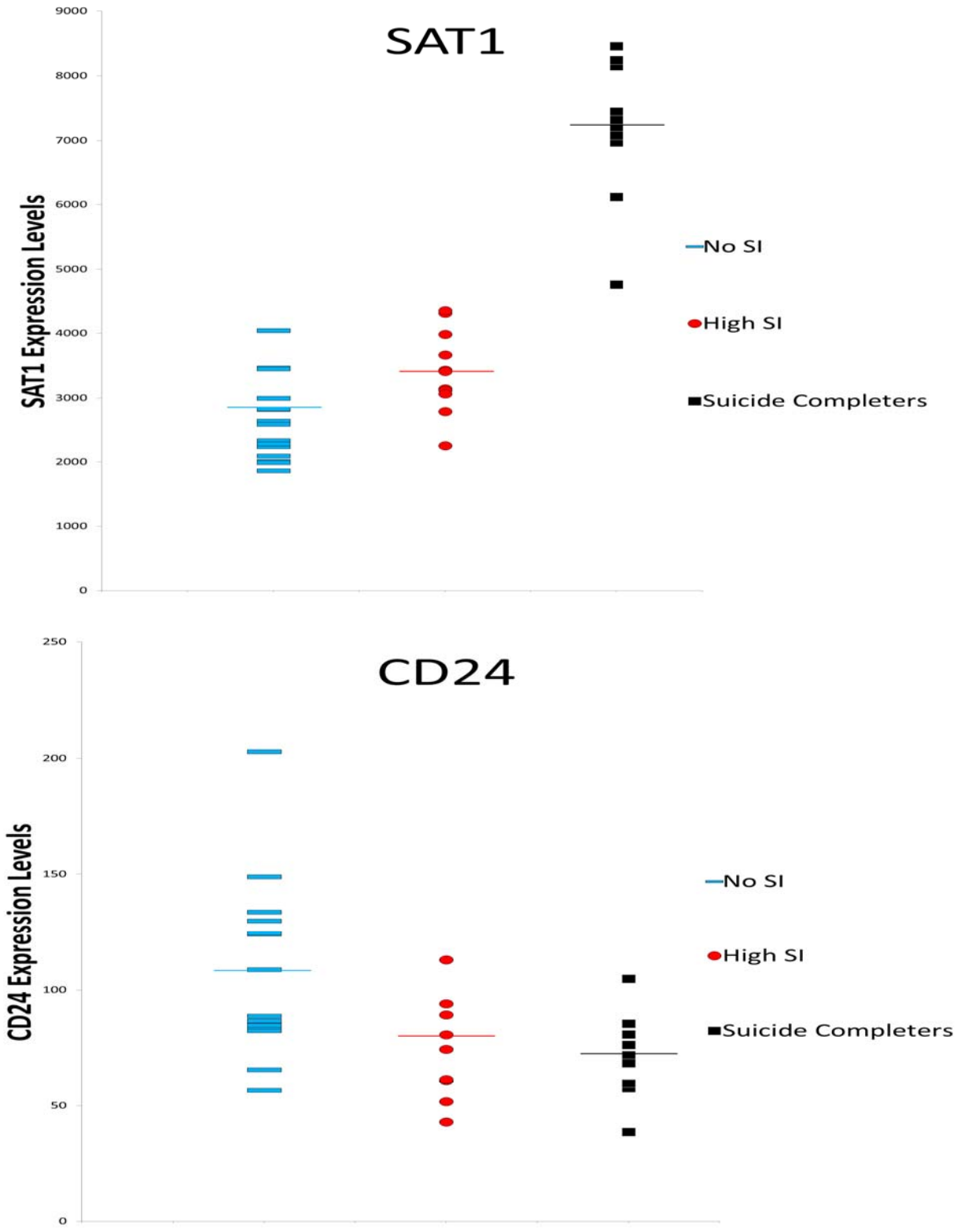
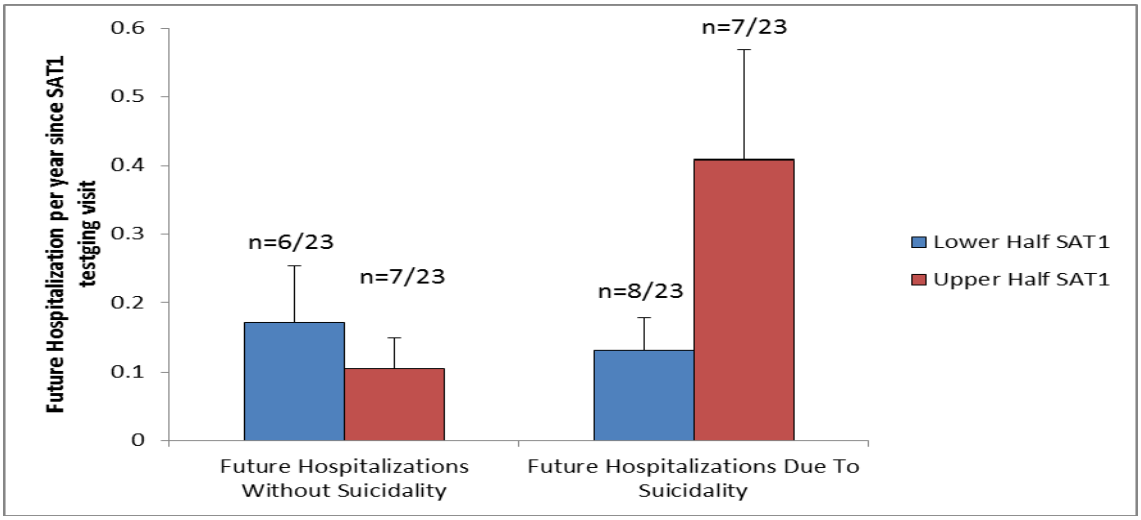
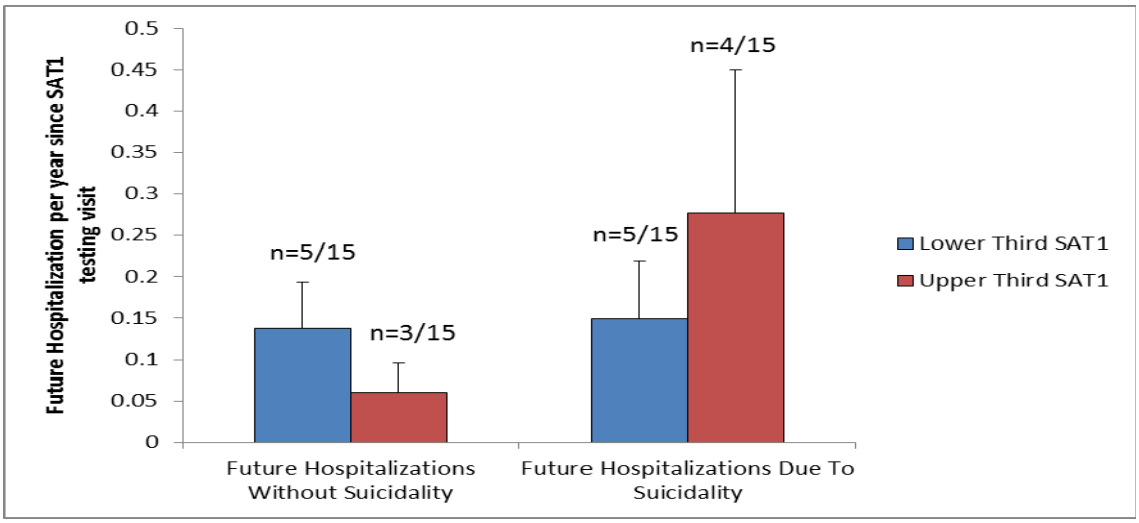


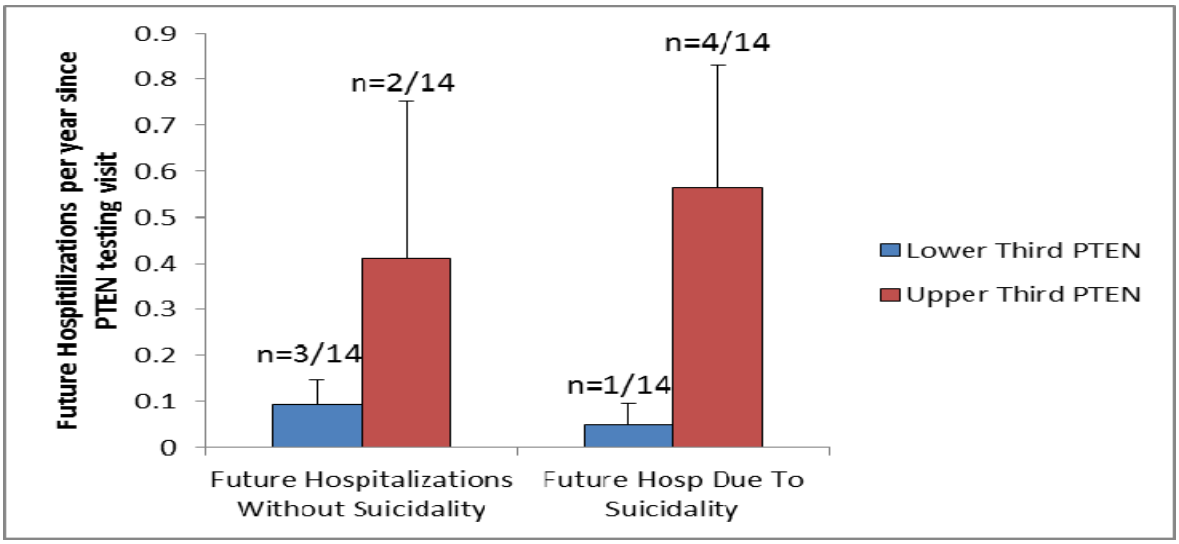
Figure S2. <u>Future</u> psychiatric hospitalizations due to suicidality in live psychosis subjects. We analyzed in 46 schizophrenia/ schizoaffective subjects (demographic data in Table S9) whether their SAT1 levels at the time of initial testing differentiated those who had subsequent hospitalizations due to suicidality in the years since the testing occurred. The results were similar to those seen in bipolar subjects (Figure 5).

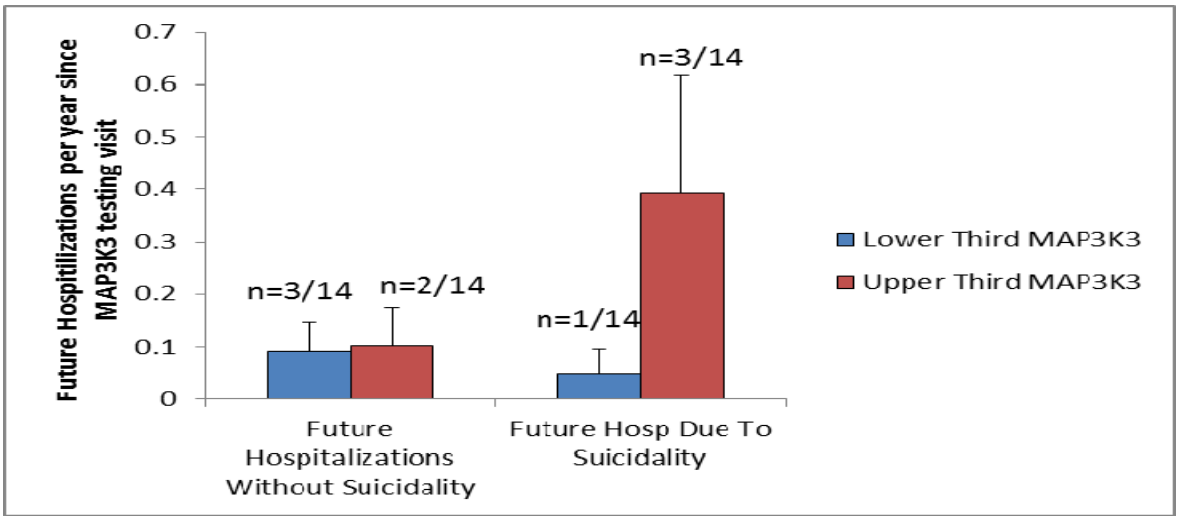




	Hospitalizations Without Suicidality t-test	Hospitalizations Due to Suicidality t-test
Upper Half SAT1 vs. Lower Half SAT1	0.2346	**0.0519**
Upper Third SAT1 vs. Lower Third SAT1	0.1251	0.2461

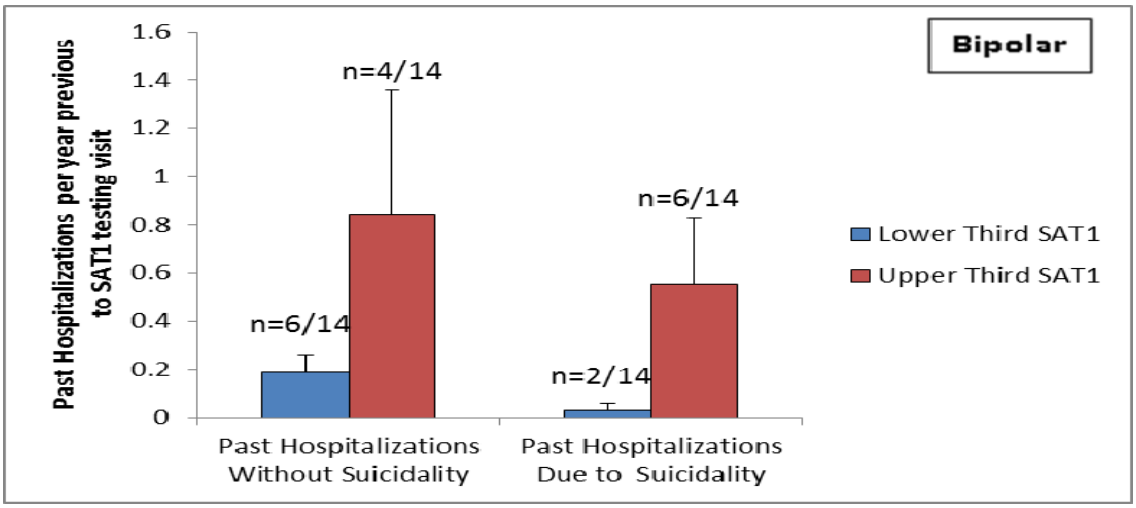
Figure S3. <u>Future</u> psychiatric hospitalizations due to suicidality in live bipolar subjects- PTEN and MAP3K3. We analyzed in 42 bipolar subjects (demographic data in Table 1) whether their PTEN and MAP3K3 levels at the time of initial testing differentiated those who had subsequent hospitalizations due to suicidality in the years since the testing occurred. The results were similar to those seen with SAT1 in bipolar subjects (Figure 5).

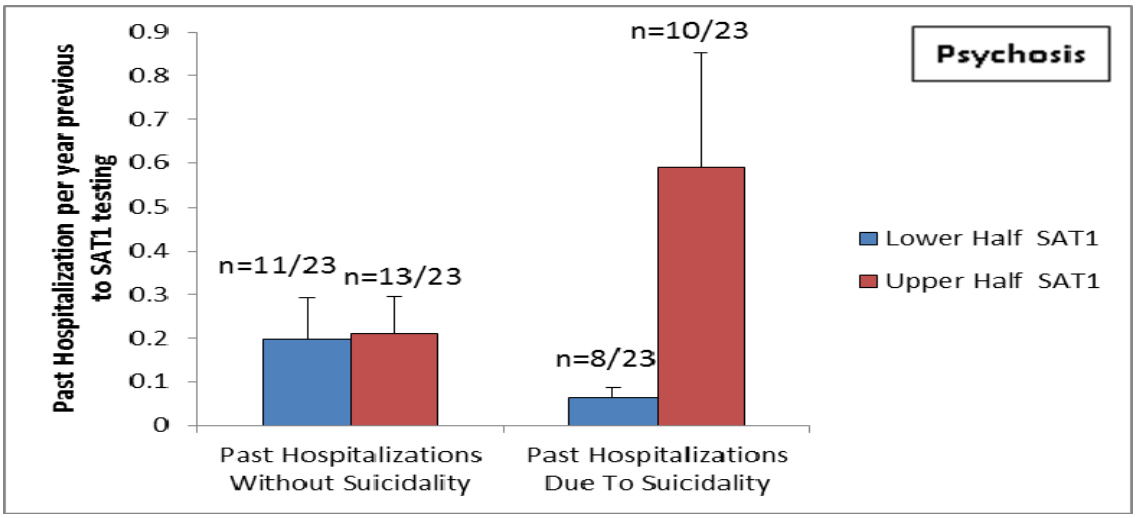




	Hospitalizations Without Suicidality (t-test)	Hospitalizations Due to Suicidality (t-test)
Upper Third PTEN vs. Lower Third PTEN	0.1856	**0.0324**
Upper Third MAP3K3 vs. Lower Third MAP3K3	0.4570	0.0724

Figure S4. <u>Past</u> psychiatric hospitalizations due to suicidality in live bipolar subjects (n=42) and live psychosis subjects (n=46). We analyzed in bipolar (demographic data in Table S10) and schizophrenia/ schizoaffective subjects (demographic data in Table S11) whether their SAT1 levels at the time of testing differentiated those who had previous hospitalizations due to suicidality in the years prior to the testing occurring. The results were similar to those seen for future hospitalizations in bipolar subjects (Figure 5) and schizophrenia/schizoaffective (Figure S2).





	Hospitalizations Without Suicidality (t-test)	Hospitalizations Due to Suicidality (t-test)
Bipolar Upper Third SAT1 vs. Lower Third SAT1	0.1108	**0.03626**
Psychosis Upper Half SAT1 vs. Lower Half SAT1	0.4564	**0.0274**

Figure S5 Clinical measures used in the multi-modal approach in Figure 6

1) Anxiety

How anxious are you right now? Compare to the worst, and to the most anxious, you ever remember feeling in your life, and to the best, least anxious you ever remember feeling.

[----------]

Least Anxious Most Anxious

2) Mood

How good is your mood right now? Compare to the worst, most depressed you ever remember feeling in your life, and to the best you ever remember feeling.

[----------]

Lowest Mood Highest Mood

3) Psychosis : averaging the scores for Hallucinations and Delusions, two key psychotic symptoms, from the Positive and Negative Symptoms Scale (PANSS).

(A) Hallucinatory Behavior: Verbal report or behavior indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory or somatic realms. **Basis for rating:** verbal report and physical manifestations during the course of interview

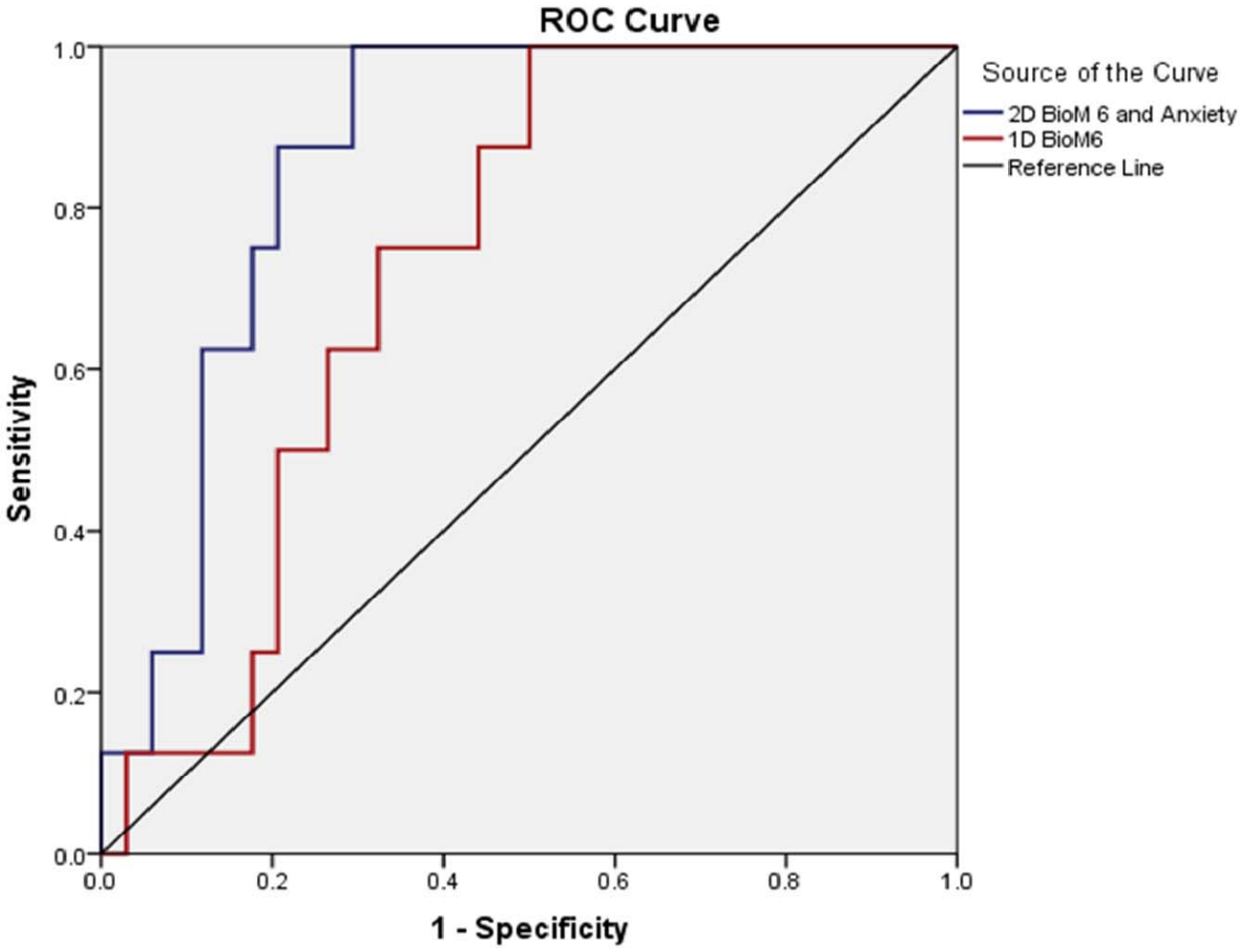
Hallucinations Score	State	Definition
1	Absent	Definition does not apply
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits
3	Mild	One or two clearly formed but infrequent hallucinations, or else a number of vague abnormal perceptions which do not result in distortions of thinking or behavior.
4	Moderate	Hallucinations occur frequently but not continuously, and the patient's thinking and behavior are affected only to a minor extent.
5	Moderate Severe	Hallucinations are frequent, may involve more than one sensory modality, and tend to distort thinking and/or disrupt behavior. Patient may have delusional interpretations of these experiences and respond to them emotionally and, on occasion, verbally as well.
6	Severe	Hallucinations are present almost continuously, causing major disruption of thinking and behavior. Patient treats these as real perceptions, and functioning is impeded by frequent emotional and verbal responses to them.
7	Extreme	Patient is almost totally preoccupied with hallucinations, which virtually dominate thinking and behavior. Hallucinations are provided a rigid delusional interpretation and provoke verbal and behavioral responses, including obedience to command hallucinations.

(B.) Delusions: beliefs which are unfounded, unrealistic, and idiosyncratic. **Basis for rating:** thought content expressed in the interview.

Delusions Score	State	Definition
1	Absent	Definition does not apply
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits
3	Mild	Presence of one or two delusions which are vague, uncrystallized, and not tenaciously held. Delusions do not interfere with thinking, social relations, or behavior.
4	Moderate	Presence of either a kaleidoscopic array of poorly formed, unstable delusions or of a few well formed delusions that occasionally interfere with thinking, social relations, or behavior.
5	Moderate Severe	Presence of numerous well-formed delusions that are tenaciously held and occasionally interfere with thinking, social relations or behavior
6	Severe	Presence of a stable set of delusions which are crystallized, possibly systematized, tenaciously held, and clearly interfere with thinking, social relations and behavior.
7	Extreme	Presence of a stable set of delusions which are highly systematized or very numerous, and which dominate major facets of the patient's life. This frequently results in inappropriate and irresponsible action, which may even jeopardize the safety of the patient or others.

Figure S6. Prediction of future psychiatric hospitalizations due to suicidality using a panel of six top markers (SAT1, PTEN, MARCKS, MAP3K3, UBA6 and MT-ND6).

We analyzed in 42 bipolar subjects whether our panel of six top biomarkers for suicidality (BioM 6), with or without an anxiety clinical measure , differentiated those who had subsequent hospitalizations due to suicidality in the years since the testing occurred. Data in each dimension was normalized to a 0-100 scale. The angle between dimensions was assumed to be 90 degrees, and a simple Pythagorean distance from origin score was calculated. The distribution of this score in the test cohort was used to generate an ROC curve for hospitalizations due to suicidality. ROC curve and detailed results are shown.



D	Test Result Variable(s)	Area Under the Curve	Std. Error	Significance	95% Confidence Interval	
					Lower Bound	Upper Bound
1D	BioM6	.732	.079	.044	.578	.886
2D	BioM6 x Anxiety	.864	.056	.002	.754	.974

1. **Le-Niculescu H, Balaraman Y, Patel S, Tan J, Sidhu K, Jerome RE *et al.* Towards understanding the schizophrenia code: an expanded convergent functional genomics approach. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 2007; 144B(2): 129-158.**

2. **Kurian SM, Le-Niculescu H, Patel SD, Bertram D, Davis J, Dike C *et al.* Identification of blood biomarkers for psychosis using convergent functional genomics. *Molecular psychiatry* 2011; 16(1): 37-58.**

3. **Le-Niculescu H, Case NJ, Hulvershorn L, Patel SD, Bowker D, Gupta J *et al.* Convergent functional genomic studies of omega-3 fatty acids in stress reactivity, bipolar disorder and alcoholism. *Translational Psychiatry* 2011; 1: e4.**

4. **Le-Niculescu H, Kurian SM, Yehyawi N, Dike C, Patel SD, Edenberg HJ *et al.* Identifying blood biomarkers for mood disorders using convergent functional genomics. *Molecular psychiatry* 2009; 14(2): 156-174.**

5. **Gaiteri C, Guilloux JP, Lewis DA, Sibille E. Altered gene synchrony suggests a combined hormone-mediated dysregulated state in major depression. *PLoS One*; 5(4): e9970.**

6. **Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD *et al.* Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proc Natl Acad Sci U S A* 2001; 98(8): 4746-4751.**

7. **Pandey GN, Dwivedi Y, Ren X, Rizavi HS, Roberts RC, Conley RR *et al.* Altered expression and phosphorylation of myristoylated alanine-rich C kinase substrate (MARCKS) in postmortem brain of suicide victims with or without depression. *J Psychiatr Res* 2003; 37(5): 421-432.**

8. **Miller BH, Zeier Z, Xi L, Lanz TA, Deng S, Strathmann J *et al.* MicroRNA-132 dysregulation in schizophrenia has implications for both neurodevelopment and adult brain function. *Proc Natl Acad Sci U S A* 2012; 109(8): 3125-3130.**

9. **Karege F, Perroud N, Burkhardt S, Fernandez R, Ballmann E, La Harpe R *et al.* Alterations in phosphatidylinositol 3-kinase activity and PTEN phosphatase in the prefrontal cortex of depressed suicide victims. *Neuropsychobiology* 2011; 63(4): 224-231.**

10. **Mudge J, Miller NA, Khrebtukova I, Lindquist IE, May GD, Huntley JJ *et al.* Genomic convergence analysis of schizophrenia: mRNA sequencing reveals altered synaptic vesicular transport in post-mortem cerebellum. *PLoS One* 2008; 3(11): e3625.**