Identification of the SAT1 Gene as a Potential Biomarker for the Prediction of Suicide in Patients Suffering from Mood Disorders

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Abstract

Background: Suicide is the consequence of a complex set of factors that results in devastation for a staggering number of people. Worldwide, suicide is responsible for over 800,000 deaths annually, while many more millions of survivors are left to cope with the repercussions of this tragedy. Despite the rampant prevalence and dire consequences, the medical community has yet to successfully establish an effective way for clinicians to anticipate a suicide attempt. However, researchers have recently identified several genes that appear altered in both suicide completers and patients suffering from suicidal ideation. These genes can be measured via RNA extraction from a sample of blood. The implications of this research are significant, for if a blood test can aid in the prediction of suicide risk, clinicians may have a feasible tool to assist in the prevention of millions of deaths.

Methods: An exhaustive search of available medical literature was conducted using Medline-OVID, PsychINFO, and Web of Science using the keywords: suicide, SAT1, and acetyltransferase. The search was narrowed to include only English language and human study articles. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating SAT1 gene expression in subjects who completed suicide or experienced suicidal ideation were included.

Results: Four studies were ultimately included in this systematic review. All four studies demonstrated significantly altered levels of SAT1 gene expression in suicide victims compared to controls. Additionally, a cohort study demonstrated increased SAT1 gene expression in live patients reporting severe suicidal ideation. These authors further determined that live patients with increased SAT1 gene expression have increased rates of hospitalizations resulting from a suicide attempt.

Conclusion: Dysregulation of SAT1 gene expression appears to be associated with suicidal behavior, though it remains unknown why this link exists and the quality of available data is very low. At this time, applications for clinical practice are minimal. However, additional research is highly warranted, as these preliminary findings suggest that SAT1 gene expression may indeed act as a biomarker and could someday aid in the prediction of a patient’s susceptibility for suicide.

Keywords: Suicide, SAT1 gene
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Identification of the SAT1 Gene as a Potential Biomarker for the Prediction of Suicide in Patients Suffering from Mood Disorders

Robin Norman

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 8, 2015

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Robin Norman lives in Hillsboro Oregon with her husband Jason. When not working, she enjoys bicycling, hiking, running, and yoga. Prior to PA school, she received her bachelor’s degree in nutrition and dietetics and worked in dermatology as a medical assistant. She has not yet decided what area of medicine she will practice in after graduation, but plans to work here in Oregon where home is.
Abstract

**Background:** Suicide is the consequence of a complex set of factors that results in devastation for a staggering number of people. Worldwide, suicide is responsible for over 800,000 deaths annually, while many more millions of survivors are left to cope with the repercussions of this tragedy. Despite the rampant prevalence and dire consequences, the medical community has yet to successfully establish an effective way for clinicians to anticipate a suicide attempt. However, researchers have recently identified several genes that appear altered in both suicide completers and patients suffering from suicidal ideation. These genes can be measured via RNA extraction from a sample of blood. The implications of this research are significant, for if a blood test can aid in the prediction of suicide risk, clinicians may have a feasible tool to assist in the prevention of millions of deaths.

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**Results:** Four studies were ultimately included in this systematic review. All four studies demonstrated significantly altered levels of SAT1 gene expression in suicide victims compared to controls. Additionally, a cohort study demonstrated increased SAT1 gene expression in live patients reporting severe suicidal ideation. These authors further determined that live patients with increased SAT1 gene expression have increased rates of hospitalizations resulting from a suicide attempt.

**Conclusion:** Dysregulation of SAT1 gene expression appears to be associated with suicidal behavior, though it remains unknown why this link exists and the quality of available data is very low. At this time, applications for clinical practice are minimal. However, additional research is highly warranted, as these preliminary findings suggest that SAT1 gene expression may indeed act as a biomarker and could someday aid in the prediction of a patient’s susceptibility for suicide.

**Keywords:** Suicide, SAT1 gene
Acknowledgements

To my brother, *Dominic Lucido*:
I miss you and think about you every day.

To *John Kee*:
Thank you for helping me better understand and cope with my brother’s death, and for working to make a difference in the lives of people suffering from depression and mood disorders. You have truly inspired me.
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<tr>
<td>SI</td>
<td>Suicidal Ideation</td>
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<tr>
<td>PSR</td>
<td>Polyamine Stress Response</td>
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<tr>
<td>HPA axis</td>
<td>Hypothalamic Pituitary Adrenal Axis</td>
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<tr>
<td>HRSD-17</td>
<td>Hamilton Rating Scale for Depression</td>
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<tr>
<td>CFG</td>
<td>Convergent Functional Genomics</td>
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<tr>
<td>SNP</td>
<td>Single Nucleotide Polymorphism</td>
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<td>MDD</td>
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Identification of the SAT1 Gene as a Potential Biomarker for the Prediction of Suicide in Patients Suffering from Mood Disorders

BACKGROUND

Suicide is the tragic consequence of a complex set of factors that results in devastation for a staggering number of people. Suicide is the tenth leading cause of death in America, with 40 600 suicides reported in 2012.\textsuperscript{1} Worldwide, suicide is responsible for over 800 000 deaths annually. In young patients aged 15-29 years, it is the third leading cause of death globally, and after cancer and heart disease, accounts for more premature deaths than any other disease.\textsuperscript{2} These numbers fail to capture the other victims of suicide: the many millions of survivors, including families, friends, and communities that are left to cope with the horrifying repercussions of this tragedy.

Despite the rampant prevalence and dire consequences, the medical community has yet to successfully establish an effective way for clinicians to anticipate a suicide attempt. A suicidal crisis results from the culmination of several complex subjective factors, including environment, personality, interpretation and reaction to acute and chronic stressors, substance abuse, portrayal of suicide in the media, personal history of suicidal ideation (SI) or attempt, family history of suicide, and access to a means.\textsuperscript{3,4} Because these subjective contributors to a suicidal state cannot be evaluated or quantified in a way that confirms intent, clinicians are at an overwhelming disadvantage when assessing a patient for suicide risk. Furthermore, patients contemplating suicide are rarely forthcoming about these thoughts, and current medical practice relies on patient reporting alone to assess risk for suicidal behavior.
With no objective measure available, the chance of identifying and helping these patients before it is too late becomes a virtually impossible endeavor. In fact, a large study recently found that 45% of suicide completers had seen a primary care provider within the month before death, and 77% of all suicide completers had contact with a primary care provider within a year of death.\(^5\)

However, promising new research is uncovering several neurobiological and physiological factors that appear to contribute to a suicidal state.\(^4\) These factors are vital to investigate, as unlike the subjective contributors to suicide, they have the potential to be objectively measured and therefore may be the key to accurate suicide prediction. One such factor is the dysfunction of the hypothalamic pituitary adrenal (HPA) axis, which results in an abnormal physiological stress response due to elevated levels of the stress hormone cortisol. Additionally, suicidal patients have an imbalance of serotonin, norepinephrine, and dopamine, neurotransmitters that are crucial for mood regulation.\(^4\) Furthermore, anatomical changes take place in a suicidal brain, particularly in the prefrontal cortex,\(^6\) the area of the brain responsible for personality, behavior, emotion and cognition. Finally, suicidal behavior is dictated in part by the victim’s genetic inheritance and epigenetic changes.\(^4\) Unfortunately, it has not yet been possible to capture these factors and cultivate them for practical suicide risk assessment in a clinical setting.

However, promising new research has identified several genes that appear to be expressed differently in suicide completers and subjects with severe SI. Remarkably, these genes can be measured via RNA extraction from a sample of blood.\(^7,8\) The implications of this research are substantial, for if a simple blood draw can aid in the
prediction of suicide risk, clinicians may have a feasible tool to assist in the prevention of millions of horrific deaths.

Of particular interest is the SAT1 (aka SSAT, SSAT-1\(^{10,13,14}\)) gene,\(^8\) which plays a significant role in the regulation of the polyamine stress response (PSR) system. Physical, emotional, and hormonal stressors elicit the PSR system, resulting in increased levels of various chemical compounds called polyamines. These compounds alter how the brain and body react to stress states.\(^9\) SAT1 is a protein coding gene located on the x chromosome.\(^10\) It codes for spermine/spermidine N1-acetyltransferase, the rate limiting enzyme in the catabolism of polyamines,\(^10\) and thus plays a direct role in controlling the PSR system.\(^9\) Alterations in SAT1 regulation subsequently result in altered levels of spermine and spermidine, potentially disrupting polyamine homeostasis and profoundly modifying the body’s response to stress. This may explain, at least in part, one of the mechanisms that contributes to a suicidal brain. If this gene is indeed altered in patients who commit suicide or have suicidal thoughts, and this gene can be measured with a blood test, an intriguing consideration arises: perhaps this gene can be used as a biomarker to aid in the prediction of a patient’s predisposition for suicidal behavior.

METHODS

An exhaustive search of available medical literature was conducted using Medline-OVID, PsychINFO, and Web of Science using the keywords: suicide, SAT1, and acetyltransferase. The search was narrowed to include only English language and human study articles. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating the regulation of the SAT1 gene in subjects who completed suicide or experienced SI were included. Relevant articles
were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE). 11

RESULTS

The initial result of the search yielded 32 articles for review. After screening relevant articles for English language and human studies, a total of four articles met inclusion criteria. These articles included two cohort studies 12,15 and two case control studies. 13,14 See Table I.

**Discovery and validation of blood markers for suicidality**

In 2013, Le-Niculescu et al 12 published a study in which 4 cohorts were analyzed: a live discovery cohort consisting of male patients diagnosed with bipolar disorder, a postmortem cohort of suicide completers, a prospective live bipolar cohort, and a prospective live psychosis cohort.

The primary study group, the live discovery bipolar cohort, consisted of male patients previously diagnosed with bipolar disorder. At the initial visit, study psychiatrists and researchers independently determined these participants had bipolar disorder using a standardized diagnostic assessment. Study participants then returned for two subsequent visits, at three and six months post diagnostic evaluation. At these visits, the patient’s level of SI was assessed using the Hamilton Rating Scale for Depression (appendix A) questionnaire (HRSD-17), and a blood sample was taken. After these two visits, researchers compared the HRSD-17 score obtained from the initial visit to the HRSD-17 score obtained at the follow up visit, and identified those patient’s who had a significant increase in SI between the three and six month visits. Nine participants were observed to have a marked increase in SI and were thus recognized as the study group.
RNA was extracted from the blood samples supplied by these nine patients. Using microarray analysis, researchers analyzed gene expression when the patient reported low or no SI, and compared these to gene expression when the patient reported high SI.\textsuperscript{12}

In order to identify those genes associated with SI, whole-genome gene expression profiling was conducted. A list of 246 overlapping genes was produced. The convergent functional genomics (CGF) approach (appendix B) was then used to prioritize each of these genes as a genomic biomarker for suicidality. The SAT1 gene was the top scorer of all of the genes analyzed. Using the CFG approach, SAT1 expression was significantly increased in the blood samples of all nine patients when they reported high SI. These same patients had lower levels of SAT1 expression when no or low SI was reported.\textsuperscript{12}

In an effort to assess whether SAT1 expression relates to completed suicide as well as increased SI, researchers then analyzed blood samples taken from nine male suicide completers using the same method of gene extraction and comparison as described above. Results showed SAT1 gene expression elevation in all nine of the blood samples extracted from the suicide victims. Notably, the increase in SAT1 expression was at least three standard deviations above the average level of expression in high SI subjects,\textsuperscript{12} suggesting that increasing levels of SAT1 expression result in increasing risk for committing suicide.

To further validate these findings, researchers conducted a prospective study examining the rate of subsequent and previous hospitalizations related to suicidal behavior in two additional cohorts composed of patients at an increased risk of suicide: a live bipolar cohort and a live psychosis cohort. Le-Niculescu et al\textsuperscript{12} found that those
patients with higher SAT1 levels in both groups were more likely to have a future hospitalization due to a suicide attempt and were more likely to have a history of these hospitalizations. As in the two previous cohorts examined, higher SAT1 levels positively correlated with suicidal behavior.\textsuperscript{12} See Table II.

Also of particular interest, these researchers assessed the utility of using a multidimensional approach, which included the objective marker of SAT1 expression in the blood combined with subjective markers provided by patient report, to aid in the prediction of future suicide related hospitalization. Using the data obtained from the examination of the prospective cohorts, researchers determined that the predictive value of SAT1 gene expression elevation was significantly enhanced with the addition of data about the patient’s perception of mood, anxiety, and psychosis.\textsuperscript{12} See Table III.

**Genetic and Epigenetic Analysis of SSAT Gene Dysregulation in Suicidal Behavior**

This study, conducted by Guipponi et al\textsuperscript{13} in 2008, aimed to validate previous findings that SSAT gene dysregulation plays a role in suicidal behavior,\textsuperscript{14} while also attempting to identify an association between suicidal behavior and certain single nucleotide polymorphisms (SNPs), substitutions in a sequence of DNA,\textsuperscript{16} located on the SSAT gene. This case control study was broken down into two distinct parts: a gene expression portion, in which researchers aimed to characterize the relationship between SSAT dysregulation and suicidal behavior, and a gene association portion, in which researchers attempted to identify the basis of SSAT expression.\textsuperscript{13}

In order to conduct the gene expression portion of the study, researchers extracted tissue samples from the brains of 20 (11 M/9 F) suicide completers, some of whom had psychiatric diagnoses and others who did not, and compared these to tissue samples taken
from the brains of 20 (10 M/9 F) subjects with no history of suicidal behavior or psychiatric illness, but had died suddenly of some other cause. The tissue samples were extracted from Brodmann’s area 11 in the prefrontal cortex, an area of the brain associated with suicide. Using quantitative PCR, RNA was extracted from these samples and analyzed for gene expression. Results showed a significant decrease in SSAT expression in the brain tissue of suicide victims with or without major psychiatric diagnoses compared to controls.

Next, researchers performed the gene association portion of the study to examine SNPs located within the SSAT gene and identify possible correlations between certain SNPs and suicidal behavior. Prior research showed that one SNP in particular, rs6526342, appeared to be associated with SSAT expression levels. To further explore this finding, two SNPs were evaluated in this study; rs6526342 and rs17286006, the latter chosen for its proximity to rs6526342. This portion of the study examined SSAT expression and SNP variations in a cohort of 88 suicide completers, and compared these findings to a cohort of 449 suicide attempters as well as a control group of 224 subjects.

Participants in the suicide attempter cohort were recruited from a psychiatric hospital after a suicide related admission. RNA was extracted from the blood samples taken from these patients and from the brain tissue of the suicide completers. The RNA extracted from the blood and brain tissue samples was examined for SSAT gene expression, also using quantitative PCR. Additionally, researchers examined SSAT gene expression levels in blood samples taken from subjects recruited from a blood donation center with no history of a suicide attempt and compared SSAT expression in these samples to the previous two cohorts. All groups were then genotyped for the
rs6526342 and rs17286006 SNPs, and the frequencies of the appearance of these SNPs were compared between clinical groups. Interestingly, even though SSAT levels varied, the SNP distributions were no different between the three groups, concluding that these particular variations have no effect on suicidal behavior.\textsuperscript{13}

Guipponi et al\textsuperscript{13} validated previous findings of an association between suicide and SSAT gene dysregulation. Additionally, this study demonstrated similar results in male and female subjects, suggesting that despite being found on the x chromosome,\textsuperscript{11} the gene is not likely sex related.\textsuperscript{13} This study also examined subjects with and without diagnoses of major psychiatric pathologies, and found that the SSAT gene was downregulated in the brain tissue of all suicide victims, regardless of diagnosed psychiatric illness. This suggests the hypothesis that abnormal expression of the gene may be an independent risk factor for suicide, regardless of accompanying psychopathology.

However, these researchers were not successful in demonstrating an association between SNPs located on the SSAT gene and suicidal behavior. Therefore, the cause of SSAT gene dysregulation remains unclear.\textsuperscript{13} See Table IV.

**Implication of SSAT by Gene Expression and Genetic Variation in Suicide and Major Depression**

This case control study conducted by Sequeira et al\textsuperscript{14} in 2006 analyzed SSAT gene expression in three areas of the brain and compared the findings between three groups; 16 suicide completers diagnosed with major depressive disorder (MDD), 18 suicide completers with no history of MDD, and 12 matched controls with no history of suicidal behavior or psychiatric illness who died suddenly by some other cause. Researchers selected three cortical brain regions previously implicated in suicide and
depression: BA8/9 (the dorsolateral prefrontal cortex),\textsuperscript{17,18} BA11 (the orbital cortex),\textsuperscript{17} and BA4 (the motor cortex).\textsuperscript{19} Additionally, researchers analyzed the relationship between the expression of an allelic variant, SSAT342A/C, and predisposition to suicide.\textsuperscript{14}

Tissues used for analysis were extracted from these three cortical regions. Using microarray, semiquantitative RT-PCR, and western blot analysis techniques, decreased SSAT gene expression was demonstrated in both suicide completer groups in all three brain areas examined compared to controls.\textsuperscript{14} The decreased expression of SSAT resulted in higher levels of spermidine/spermine N\textsuperscript{1}-acetyltransferase,\textsuperscript{14} the rate limiting enzyme in the PSR system,\textsuperscript{10} in the suicide groups. This finding was especially pronounced in the MDD suicide group compared to the non-MDD suicide group, suggesting a possible role of SSAT gene dysregulation in the pathophysiology of depression as well as suicide. Additionally, the discovery of increased levels of spermidine/spermine N\textsuperscript{1}-acetyltransferase in the suicide completer group provides additional evidence linking PSR system dysfunction to suicidal behavior.\textsuperscript{14} See Table V.

Next, researchers examined an allelic variant of interest, SSAT342A/C. The authors noted that SSAT expression was significantly affected in subjects with the SSAT342A/C allele, observing that patients with the allele had a higher rate of suicide. To further explore this connection, researchers genotyped samples from 181 suicide completers and 80 controls, specifically checking for this allele. This analysis demonstrated a higher frequency of this allelic variant among suicide cases. Subjects whose genotype expressed the SSAT342A/C variant were more likely to have committed
suicide, while those subjects without the variant were less likely to have died by suicide.\textsuperscript{14}

**Profiling Brain Expression of the Spermidine/Spermine N\textsuperscript{1}-Acetyltransferase 1 (SAT1) Gene in Suicide**

This case control and cohort study conducted in 2008 by Klempan et al\textsuperscript{15} endeavored to expand upon the findings discussed by Sequeira et al\textsuperscript{14} by identifying additional brain areas associated with SAT1 gene dysregulation, while attempting to validate previous findings associating altered SAT1 expression and a dysfunctional PSR system with suicidal behavior. In addition to analyzing 17 new brain regions for SAT1 expression, the authors also attempted to replicate previous findings of SSAT expression abnormalities in suicide victims by investigating genetic expression in a previously unexamined sample of suicide completers.\textsuperscript{15} See Table VI.

This study utilized a design similar to Sequeira et al\textsuperscript{14} and examined three groups: a suicide completers group whose subjects had been previously diagnosed with MDD, a suicide completers group not diagnosed with MDD, and a control group. The subjects in this study represented a cohort that overlapped with the cohort examined by Sequiera et al.\textsuperscript{14} Seventeen areas of the brain were identified and tissue samples from each area were collected for analysis. Using microarray and RT-PCR analysis, all but two brain regions showed lower levels of SAT1 expression in all suicide completers. Of these, five cortical brain regions were statistically significant (ba4, ba11, ba20, ba21, ba44).\textsuperscript{15} Similar to the findings from Sequeira et al,\textsuperscript{14} down regulation of the SAT1 gene was significantly more pronounced in the brain tissue samples of MDD suicide completers than non-MDD suicide completers.\textsuperscript{14,15}
Additionally, Klempan et al\textsuperscript{15} examined levels of SAT1 gene expression in a previously unexamined German cohort. Study subjects consisted of a group of five suicide completers diagnosed with MDD (3 M/2 F) and 10 non-suicide controls (7 M/3 F). SAT1 expression was evaluated using tissue samples from two cortical brain regions: ba11 and ba17.\textsuperscript{15} Using the RT-PCR method, both regions demonstrated significantly reduced levels of SAT1 expression in depressed individuals who died by suicide.\textsuperscript{15}

This study demonstrated SAT1 gene downregulation in the brain tissue of suicide completers in at least five out of the 17 cortical brain regions examined.\textsuperscript{15} These researchers concluded that changes in polyamine metabolism, which occurs as a direct result of genetic coding, is correlated with suicide completion.\textsuperscript{15} These findings were especially pronounced in patients suffering from MDD.\textsuperscript{15} Furthermore, this study validated previous findings that the SAT1 gene is altered in suicide completers.\textsuperscript{13,14,15}

DISCUSSION

Summary of Findings

These studies\textsuperscript{12,13,14,15} certainly suggest that errors in SAT1 genetic coding, resulting in an imbalance of polyamine levels, plays a key role in suicidality. All four studies\textsuperscript{12,13,14,15} examined in this review successfully identified alterations in SAT1 gene expression in suicide completers.

Furthermore, the discovery of elevated SAT1 gene levels in the blood samples of live patients with SI by Le-Niculescu et al\textsuperscript{12} is particularly encouraging, as this gene may indeed act as a biomarker for the prediction of suicide. These authors also demonstrated an intriguing correlation between high SAT1 levels and hospitalizations due to suicidal behaviors. Additionally, these researchers confirmed that using a multidimensional
approach that includes SAT1 gene expression analysis in combination with subjective markers when assessing a patient for SI increases the likelihood of accurately predicting future suicide related hospitalizations.\textsuperscript{12}

Sequeira et al\textsuperscript{14} exposed and expounded upon the hypothesis that an imbalance of PSR enzymes relates to a dysfunctional stress response,\textsuperscript{9,14} a known factor for increased risk of suicide.\textsuperscript{4} These researchers also identified a genetic variant that appears to be connected to suicide, further implicating a genetic component to this behavior.\textsuperscript{14}

While the research presented is preliminary and significantly limited by study design, small sample size and a lack of diversity,\textsuperscript{12,13,14,15} the results have implications furthering the understanding of the pathophysiology of suicide and for the possible development of an accurate and practical blood test to track suicidal risk.

**Implications for Clinical Practice**

This research identifies a correlation between SAT1 gene abnormalities and suicide. However, research is still in the most preliminary of stages and at this point not particularly applicable to clinical practice. Only a correlation between SAT1 gene dysregulation and suicide was demonstrated,\textsuperscript{12,13,14,15} and this correlation does not definitively prove that the two are linked. No study has yet explained why these changes occur, and it remains unclear if these genetic alterations result in an increased risk of suicide, or if a predisposition to suicide results in these alterations. Even if absolute causation was identified, no blood test yet exists in a clinical setting that specifically examines SAT1 gene expression.

Furthermore, considering the inherent complexities associated with predicting another person’s future behavior, especially regarding something as complex and
impulsive\textsuperscript{20} as suicide, combined with the general challenges of practicing medicine, it is highly unlikely that suicide will ever be totally predictable. As previously discussed, suicide is the result of several objective and subjective factors. The subjective factors that are contributory to a suicidal state cannot be definitively measured. However, the implications of this research are still substantial for health care providers.

Perhaps the most important finding for clinicians working with patients suffering from mood disorders is the evidence presented by Le-Niculescu et al\textsuperscript{12} regarding the efficacy of using a multidimensional approach when assessing patients for suicide risk. These researchers found that utilizing SAT1 gene expression as part of a multidimensional approach greatly increased the likelihood of accurately predicting a suicide related hospitalization. In fact, objective measurement of SAT1 gene expression in the blood, combined with subjective reports, resulted in 95\% accuracy rate for predicting future suicide related hospitalizations for patients with high SAT1 expression, high levels of anxiety, perceptions of psychosis, and depressed mood.\textsuperscript{12} While it is unlikely that a single questionnaire, blood test, or study will ever predict with total confidence something as complex as suicide, these findings suggest that utilizing multiple tools and approaches results in a higher likelihood of accurately predicting, and therefore preventing, these deaths.

Likewise, a genetic biomarker may someday be immensely helpful to clinicians for use in tracking disease progression and response to therapy, something that is already being done with biomarkers for diseases like cancer.\textsuperscript{21} The clinical implications of this are considerable, for if a clinician is able to objectively assess a patient’s baseline suicide
risk and then track this patient’s response to therapy, treatment regimens could be vastly improved and many lives could be saved.

Also of essential use for clinicians, especially in these preliminary stages of research, is the general awareness this research raises regarding suicide. The lack of understanding surrounding suicide and mental health disease is alarming. Many people in the general public and healthcare providers alike still consider suicide a selfish personal choice, and regard mental health disease as a personal failing and problem that can be cured with willpower alone. Studies such as these, that link mental illness to genetics and neurobiological factors, provide enlightenment and education for people to better understand these diseases. This type of awareness is a key factor in reducing stigma and stamping out damaging and uninformed perceptions about suicide. These studies, and several like them, are gaining wide attention in the mainstream media, bringing awareness to the general public and modifying outdated clinical practice.

**Study Limitations**

The studies, while promising, have major limitations and flaws. Based on the GRADE criteria, the overall quality of the studies reviewed is very low. The most pronounced limitation is design as the studies were either cohort or case control. Therefore, though a correlation was shown between SAT1 gene expression, suicide, and SI, there is no evidence to show that the genetic alterations observed in study subjects directly influenced their suicidal behavior. Additionally, there is no explanation as to why these changes occur, and while SAT1 dysregulation certainly appears to occur in suicidal patients, it is unclear if these alterations cause suicidal behavior or if suicidal behavior is a consequence of these alterations. Furthermore, all
the sample sizes were small and nearly all the participants were white, with a majority being male.\textsuperscript{12,13,14,15}

Because of the postmortem nature of the majority of the studies, concern for selection, performance, and attrition bias is low. The outcomes measured in the Guipponi et al,\textsuperscript{13} Sequeira et al,\textsuperscript{14} and Klempan et al\textsuperscript{15} studies are definitive and the variables examined are not easily manipulated. The Le-Niculescu et al\textsuperscript{12} study is at a slightly higher risk for bias as the study dealt with live cohorts and a peripheral marker, blood instead of brain tissue samples, however the risk still remains relatively low as an objective factor, SAT1 regulation, was the main outcome examined.

Also, there is a slight risk for recall bias in the research conducted by Sequeira et al.\textsuperscript{14} The study examined two groups of suicide completers, one group consisted of subjects diagnosed with MDD and the other group consisted of subjects not diagnosed with MDD. These diagnoses were obtained via interviews with a proxy in a postmortem psychological autopsy,\textsuperscript{14} therefore raising the concern that these diagnoses are not accurate.

Additionally, multiple variations between studies were identified throughout this literature review. While these variations are not of great relevance to the conclusions presented, it is important to acknowledge and discuss these variations in terms of general study limitations. The most conspicuous and essential variation was that Le-Niculescu et al\textsuperscript{12} demonstrated that increased expression of the SAT1 gene is associated with suicide,\textsuperscript{12} whereas the other three studies found decreased SAT1 gene expression is associated with suicide.\textsuperscript{13,14,15} Several possible explanations may explain these findings. First, Guipponi et al,\textsuperscript{13} Sequeira et al,\textsuperscript{14} and Klempan et al\textsuperscript{15} conducted experiments in which RNA
extracted from brain tissue samples was used to evaluate gene expression, while Le-
Niculescu et al\textsuperscript{12} used peripheral blood cells for RNA extraction to assess gene
expression. It is certainly possible, and even likely, that gene expression profiles differ
between brain tissue and blood cells. Therefore, the finding that the SAT1 expression is
altered depending on the type of cell used for RNA extraction is not necessarily a
contradictory or even surprising finding. Next, the research presented by Le-Niculescu et
al\textsuperscript{12} is 18 months old, whereas the research presented by Guipponi et al\textsuperscript{13} and Klempan et
al\textsuperscript{15} is six years old, and the research published by Sequeira et al\textsuperscript{14} is eight years old. The
ability to examine gene expression is relatively new, and significant innovations in this
field are common. Considering the time lapse between studies, modifications in
experimentation between study publications may account for these seemingly conflicting
results. Finally, the studies analyzed in this review all employed different methods for
RNA quantification.\textsuperscript{12,13,14,15} Le-Niculescu et al\textsuperscript{12} used microarray analysis, Guipponi et
al\textsuperscript{13} used quantitative PCR, Sequeira et al\textsuperscript{14} used microarray analysis, semiquantitative
RT-PCR, and western blot, and Klempan et al\textsuperscript{15} used microarray analysis and RT-PCR.
The divergent findings presented in this review may well be attributed to the differing
methods of gene expression and profiling used by study authors. (Lisa Sardinia, PhD, JD,
email communication, December 30, 2014).

Another variation was that Sequeira et al\textsuperscript{14} reported identifying an allelic variant
of the SAT1 gene that appears to increase predisposition to suicide. This finding was not
replicable by Guipponi et al.\textsuperscript{13}

Finally, Sequeira et al\textsuperscript{14} and Klempan et al\textsuperscript{15} found SSAT expression to be
markedly altered between suicide completers with MDD and suicide completers without
MDD. However, Guipponi et al\textsuperscript{13} reported that SSAT is downregulated equally across all psychopathologies, implying no increased risk for suicide in patients suffering from MDD.

**Areas of Future Research**

Several areas for potential research are identified by this review. First, all four studies\textsuperscript{12,13,14,15} implicate the PSR system in suicidal behavior, yet this system is poorly understood. The relationship between the genes that control the PSR system and its role in suicidal behavior is intriguing, as preliminary research shows that PSR system dysfunction contributes significantly to the altered stress reactions implicated in suicide.\textsuperscript{9} Therefore, it is important to further investigate why and how this system is controlled and what factors contribute to it’s malfunction in a patient suffering from SI. Further research exploring how this system operates may contribute significantly to better understanding suicidal behavior.

Another intriguing area for future research is the examination of SAT1 gene expression in live subjects in response to therapy. The utility of a biomarker is not only its use in tracking risk for a particular disease, but also to gauge effectiveness of therapy and response to treatment. It is fundamental to explore the utility of the SAT1 gene in this capacity.

Finally, before the clinical applicability of using the SAT1 gene as a predictor of suicide can be determined, these studies need to be replicated in much larger and more diverse populations. Researchers must conduct additional studies using standardized methods of gene extraction and expression that yield similar results. Also, more studies
must be performed examining SAT1 expression in the blood specifically, rather than brain tissue.

CONCLUSION

SAT1 gene regulation is altered in patients who commit suicide and have high SI according to the data presented in these studies,\textsuperscript{12,13,14,15} implicating genetics and the PSR system in suicidal behavior. Research is in the most preliminary of stages, and currently there is no explanation as to why these defects occur. While the SAT1 gene may indeed act as a biomarker for susceptibility to suicidal behavior, no blood test identifying SAT1 expression currently exists outside of a research setting, so implications for clinical practice are minimal. However, with additional research furthering the understanding of SAT1 dysregulation in suicide, the potential exists for the development of a blood test identifying SAT1 expression abnormalities. This test may someday be a key factor in determining suicide risk.

The successful validation of the SAT1 gene as a biomarker for suicide prediction relies on several areas of additional research. First, identifying the role the PSR system plays in genetics and the role genetics play in the PSR system is fundamental not only to the development of an accurate and reliable blood test for suicide prediction, but also in understanding suicidal behavior. Second, examining the fluctuations of SAT1 gene expression in live patients in response to therapy will be the next step in developing these blood markers for clinical applicability. Finally, these studies need to be replicated using standardized methods in larger and more diverse patient populations.
References


### Table I. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Downgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study Design</td>
<td>Limitations</td>
</tr>
<tr>
<td><strong>Mortality (Suicide)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le-Niculescu et al(^\text{12})</td>
<td>Cohort</td>
<td>Not serious</td>
</tr>
<tr>
<td>Guipponi et al(^\text{13})</td>
<td>Case Control</td>
<td>Not serious</td>
</tr>
<tr>
<td>Sequeira et al(^\text{14})</td>
<td>Case Control</td>
<td>Serious(^d)</td>
</tr>
<tr>
<td>Klempan et al(^\text{15})</td>
<td>Cohort</td>
<td>Serious(^f)</td>
</tr>
<tr>
<td><strong>Suicidal Ideation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le-Niculescu et al(^\text{12})</td>
<td>Cohort</td>
<td>Not serious</td>
</tr>
<tr>
<td><strong>Suicide related hospitalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le-Niculescu et al(^\text{12})</td>
<td>Cohort</td>
<td>Not serious</td>
</tr>
</tbody>
</table>

\(^a\)Blood samples were used as biomarkers to measure SAT1 expression
\(^b\)The sample size is small (n=9)
\(^c\)Concern for recall bias: one study group includes non-depressed suicide completers and the other includes depressed suicide completers. These diagnoses were obtained postmortem via psychological autopsy, therefore relied upon by interviews with a proxy resulting in high risk of recall bias
\(^d\)The sample size is small (n=20)
\(^e\)The sample size is small (n=24)
\(^f\)No statistical analysis provided regarding SAT1 expression in the control group compared to the sample group
\(^g\)The sample size is small (n=5)
\(^h\)The sample size is small (n=42 prospective bipolar group/n=46 prospective psychosis group)
### Table II – VI. Summary of Findings

#### Table II.
Le-Niculescu et al\(^1\)\(^2\)

<table>
<thead>
<tr>
<th>Study group</th>
<th>SSAT mean expression</th>
<th>P value</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide Completers (n=8)</td>
<td>7171.51</td>
<td>0.0057</td>
<td>Very Low</td>
<td>Critical</td>
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<tr>
<td>High Suicidal Ideation (n=9)</td>
<td>3214.37</td>
<td>0.0057</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Suicidal Ideation (n=9)</td>
<td>2642.97</td>
<td>0.0057</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Table III.
Le-Niculescu et al\(^1\)\(^2\)

<table>
<thead>
<tr>
<th>Number of Dimensions</th>
<th>Test Result Variable</th>
<th>Area Under Curve</th>
<th>Standard Deviation Error</th>
<th>Significance</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1D</td>
<td>SAT1</td>
<td>0.640</td>
<td>0.086</td>
<td>0.224</td>
<td>.471 .808</td>
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<tr>
<td>2D</td>
<td>SAT1+anxiety</td>
<td>0.798</td>
<td>0.068</td>
<td>0.089</td>
<td>.665 .931</td>
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<tr>
<td>3D</td>
<td>SAT1+anxiety+mood</td>
<td>0.813</td>
<td>0.066</td>
<td>0.006</td>
<td>.683 .942</td>
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<tr>
<td>4D</td>
<td>SAT1+anxiety+mood+psychosis</td>
<td>0.835</td>
<td>0.066</td>
<td>0.004</td>
<td>.706 .964</td>
</tr>
</tbody>
</table>

#### Table IV.
Guipponi et al\(^1\)\(^4\)

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>SSAT Expression</th>
<th>P-value</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide completers (n=20)</td>
<td>-0.497 ± 0.11</td>
<td>0.007</td>
<td>Very Low</td>
<td>Critical</td>
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<tr>
<td>Control group (n=20)</td>
<td>0.0721±0.15</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Table V.
Sequeira et al\(^1\)\(^4\)

<table>
<thead>
<tr>
<th>Brain Area</th>
<th>Relative SSAT expression</th>
<th>Brain Area</th>
<th>Relative SSAT expression</th>
<th>Brain Area</th>
<th>Relative SSAT expression</th>
<th>P value</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA4</td>
<td>FC: -1.6</td>
<td>BA4</td>
<td>FC: -1.6</td>
<td>BA4</td>
<td>FC: -1.4</td>
<td>P&lt;.001</td>
<td>Critical</td>
</tr>
<tr>
<td>B9/8</td>
<td>FC: -1.4</td>
<td>B9/8</td>
<td>FC: -1.4</td>
<td>B9/8</td>
<td>FC: -1.4</td>
<td>P&lt;.05</td>
<td></td>
</tr>
<tr>
<td>BA11</td>
<td>FC: -1.8</td>
<td>BA11</td>
<td>FC: -1.8</td>
<td>BA11</td>
<td>FC: -1.4</td>
<td>P&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MDD, major depressive disorder; FC, fold change; BA, Brodmann area

#### Table VI.
Klempan et al\(^1\)\(^5\)

<table>
<thead>
<tr>
<th>Depressed Suicide Completers (n=5)</th>
<th>Controls (n=10)</th>
<th>P value</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain area</td>
<td>SSAT Expression</td>
<td>Brain area</td>
<td>SSAT Expression</td>
</tr>
<tr>
<td>BA11</td>
<td>FC: -1.5</td>
<td>BA11</td>
<td>P=0.05</td>
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<tr>
<td>BA17</td>
<td>FC: -1.6</td>
<td>BA17</td>
<td>P=0.05</td>
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</table>

Abbreviations: FC, fold change; BA, Brodmann area
### Appendix A
The Hamilton Depression Rating Scale 17

Patient Name: ________________________________ Date: __________________

#### Hamilton Rating Scale for Depression (17-items)

**Instructions:** For each item select the “cue” which best characterizes the patient during the past week.

1. **Depressed Mood**
   - (sadness, hopelessness, helplessness, worthlessness)
   - 0 Absent
   - 1 These feeling states indicated only on questioning
   - 2 These feeling states spontaneously reported verbally
   - 3 Communicates feeling states nonverbally, i.e., through facial expression, posture, voice and tendency to weep
   - 4 Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and nonverbal communication

2. **Feelings of Guilt**
   - 0 Absent
   - 1 Self-reproach, feels he has let people down
   - 2 Ideas of guilt or rumination over past errors or sinful deeds
   - 3 Present illness is a punishment. Delusions of guilt
   - 4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **Suicide**
   - 0 Absent
   - 1 Feels life is not worth living
   - 2 Wishes he were dead or any thoughts of possible death to self
   - 3 Suicide ideas or gesture
   - 4 Attempts at suicide (any serious attempt rates 4)

4. **Insomnia - Early**
   - 0 No difficulty falling asleep
   - 1 Complains of occasional difficulty falling asleep i.e., more than 1/2 hour
   - 2 Complains of nightly difficulty falling asleep

5. **Insomnia - Middle**
   - 0 No difficulty
   - 1 Patient complains of being restless and disturbed during the night
   - 2 Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. **Insomnia - Late**
   - 0 No difficulty
   - 1 Waking in early hours of the morning but goes back to sleep
   - 2 Unable to fall asleep again if gets out of bed

7. **Work and Activities**
   - 0 No difficulty
   - 1 Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies
   - 2 Loss of interest in activity; hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
   - 3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores.
   - 4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unsupervised.

8. **Retardation**
   - (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
   - 0 Normal speech and thought
   - 1 Slight retardation at interview
   - 2 Obvious retardation at interview
   - 3 Interview difficult
   - 4 Complete stupor

9. **Agitation**
   - 0 None
   - 1 “Playing with” hand, hair, etc.
   - 2 Hand-wringing, nailbiting, biting of lips

10. **Anxiety - Psychic**
    - 0 No difficulty
    - 1 Subjective tension and irritability
    - 2 Worrying about minor matters
    - 3 Apprehensive attitude apparent in face or speech
    - 4 Fears expressed without questioning

11. **Anxiety - Somatic**
    - 0 Absent
    - 1 Physiological concomitants of anxiety such as:
      - 0 Mild Gastrointestinal - dry mouth, wind, indigestion
      - 2 Moderate diarreha, cramps, belching
      - 3 Severe Cardiovascular - palpitations, headaches
    - 4 Incapacitating Respiratory - hyperventilation, sighing
    - 5 Urinary frequency
    - 6 Sweating

12. **Somatic Symptoms - Gastrointestinal**
    - 0 None
    - 1 Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
    - 2 Difficulty eating without staff urging. Requests or requires laxatives or medications for bowels or medication for G.I. symptoms.

13. **Somatic Symptoms - General**
    - 0 None
    - 1 Heaviness in limbs, back or head, backaches, headache, muscle aches, loss of energy and fatigability
    - 2 Any clear-cut symptom rates 2

14. **Genital Symptoms**
    - 0 Absent
    - 1 Mild Symptoms such as: loss of libido
    - 2 Severe Menstrual disturbances

15. **Hypochondriasis**
    - 0 Not present
    - 1 Self-absorption (bodily)
    - 2 Preoccupation with health
    - 3 Frequent complaints, requests for help, etc.
    - 4 Hypochondriastic delusions

16. **Loss of Weight**
    - A. When Rating by History:
      - 0 No weight loss
      - 1 Probable weight loss associated with present illness
      - 2 Definite (according to patient) weight loss
    - B. On Weekly Ratings by Ward Psychiatrist, When Actual Changes are Measured:
      - 0 Less than 1 lb. weight loss in week
      - 1 Greater than 1 lb. weight loss in week
      - 2 Greater than 2 lb. weight loss in week

17. **Insight**
    - 0 Acknowledges being depressed and ill
    - 1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
    - 2 Denies being ill at all

**Total Score:**
Appendix B
Convergent Functional Genomics Model For Identification and Prioritization of Suicide Biomarkers

Bipolar Subjects Whole Blood Differentially Expressed in no SI vs. High SI (6 points)

Human Postmortem Brain Evidence (4 points)

Human Genetic Evidence-association, CNV, or linkage (2 points)

Candidate Gene Biomarker