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Predicting Suicidal Behavior by an Accurate Monitoring of RNA Editing Biomarkers in Blood Samples

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Abstract : Predicting suicidal behaviors is one of the most complex challenges of daily psychiatric practices. Today, suicide risk prediction using biological tools is not validated and is only based on subjective clinical reports of the at-risk individual. Therefore, there is a great need to identify biomarkers that would allow early identification of individuals at risk of suicide. Alterations of adenosine-to-inosine (A-to-I) RNA editing of neurotransmitter receptors and other proteins have been shown to be involved in etiology of different psychiatric disorders and linked to suicidal behavior. RNA editing is a co- or post-transcriptional process leading to a site-specific alteration in RNA sequences. It plays an important role in the epi transcriptomic regulation of RNA metabolism. On postmortem human brain tissue (prefrontal cortex) of depressed suicide victims, Alcediag found specific alterations of RNA editing activity on the mRNA coding for the serotonin 2C receptor (5-HT2cR). Additionally, an increase in expression levels of ADARs, the RNA editing enzymes, and modifications of RNA editing profiles of prime targets, such as phosphodiesterase 8A (PDE8A) mRNA, have also been observed. Interestingly, the PDE8A gene is located on chromosome 15q25.3, a genomic region that has recurrently been associated with the early-onset major depressive disorder (MDD). In the current study, we examined whether modifications in RNA editing profile of prime targets allow identifying disease-relevant blood biomarkers and evaluating suicide risk in patients. To address this question, we performed a clinical study to identify an RNA editing signature in blood of depressed patients with and without the history of suicide attempts. Patient's samples were drawn in PAXgene tubes and analyzed on Alcediag's proprietary RNA editing platform using next generation sequencing technology. In addition, gene expression analysis by quantitative PCR was performed. We generated a multivariate algorithm comprising various selected biomarkers to detect patients with a high risk to attempt suicide. We evaluated the diagnostic performance using the relative proportion of PDE8A mRNA editing at different sites and/or isoforms as well as the expression of PDE8A and the ADARs. The significance of these biomarkers for suicidality was evaluated using the area under the receiver-operating characteristic curve (AUC). The generated algorithm comprising the biomarkers was found to have strong diagnostic performances with high specificity and sensitivity. In conclusion, we developed tools to measure disease-specific biomarkers in blood samples of patients for identifying individuals at the greatest risk for future suicide attempts. This technology not only fosters patient management but is also suitable to predict the risk of drug-induced psychiatric side effects such as iatrogenic increase of suicidal ideas/behaviors.

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