THE HARTWELL FOUNDATION

2015 Individual Biomedical Research Award

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Blood-Based Diagnostic Test for Anxiety Disorder

Anxious temperament is an important childhood risk for the development of clinical anxiety disorder and clinical depression. This anxious disposition is identifiable early in life and is stable during development. Infants with this temperament display heightened distress and motor reactivity to novel stimuli. As toddlers and young children they avoid social encounters and tend to withdraw from unfamiliar social situations making them less assertive and prone to rejection by their peers. Affected children are socially inhibited, have fewer friends, report greater anxiety and loneliness, and endure negative self-perceptions. Unfortunately it can take on average 8-10 years before severe cases are correctly diagnosed. Strikingly, less than 20% of affected children in the U.S. receive the needed treatment for their cognitive illness and misdiagnosis often leads to suicide, which is now the 2nd leading cause of death of American youth aged 10-24 years, after accidents. Determining the molecular mechanisms underlying the development of childhood anxious temperament is critical for development of effective therapies for altering the development of serious anxiety and depressive disorders associated with poor mental health. Since human postmortem brain tissue from children with anxiety-related phenotyping and brain imaging does not exist, new insights into the origins of anxiety and depressive disorders must be derived from translatable animal models. Fortunately, a translatable non-human primate model of anxious temperament is available, providing a means to relate structural and functional similarities in the neural circuits that mediate the childhood risk for the disorder. Using this model, Reid proposes to develop a blood-based diagnostic test for childhood anxiety disorder based upon observed changes in genetic expression of key brain chemicals. In preliminary data derived from 23 male monkeys, he was able to identify that anxious temperament was associated with epigenetic changes due to the addition of methyl groups in DNA. He found that certain enzymes responsible for DNA methylation are altered in anxiety, influencing the pattern of DNA methylation and genetic expression of genes. He expects that a more systematic approach will identify novel biochemical markers of anxiety. To do so, he will correlate DNA methylation and altered gene expression patterns in discrete brain regions of young monkeys who were previously diagnosed with anxious temperament using neuroimaging and behavioral phenotypes. To identify a surrogate blood-based biomarker of anxiety, he will map the differences in gene expression in the monkey brain and compare it with blood samples from children diagnosed with varying levels of anxiety. If Reid is successful, it will be possible for the first time to quickly confirm the diagnosis of childhood anxiety using a blood-based diagnostic test.