THE HARTWELL FOUNDATION

2007 Individual Biomedical Research Award

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Dysregulation of Ca^{2+} Signaling in Autism

Autism is a lifelong neurodevelopmental disorder characterized by impaired social interaction, problems with verbal and nonverbal communication, and unusual, repetitive, or severely limited activities and interests, all starting before a child is three years old. Milder, related forms of the disorder include Asperger syndrome, Rett syndrome, childhood disintegrative disorder, and pervasive developmental disorder, which when all taken together, make up autism spectrum disorder (ASD). Since 1994, ASD has reached epidemic proportions in the United States and the increase is not attributable to changes in diagnostic criteria. The CDC estimates 3-6 children out of every 1,000 will have the disorder, with males four times more likely to have ASD than females. ASD is now second in frequency only to mental retardation. There is no single known cause or known cure, and children do not “outgrow” ASD. However, recent studies show that very early diagnosis with vigorous "social" intervention can lead to significantly improved outcomes. With the right services and support, people with ASD can live full, healthy and meaningful lives; the staggering reality is the growing estimated $35 billion per year societal cost for lifetime care of all affected individuals. Genetics is a critical factor in predisposing children to ASD and mutations in many genes seem to contribute to the same phenotype: a childhood disease, which affects the development of the human brain by disrupting synaptic maturation and neural connectivity, as well as nerve signal transmission. Capitalizing on recent genetic and anatomical findings that suggest genes that code for proteins involved in brain signals communicated by calcium (Ca^{2+}) are abnormal in autism, Dr. Rajadhyaksha proposes to determine how the abnormal genes cause aberrant neuronal Ca^{2+} signaling during early brain development. She seeks to learn how the altered structures in the branched projections of the neurons in autism ultimately contribute to the characteristic deficits seen in ASD. Rajadhyaksha intends to quantitate the structural and functional effects of introducing these mutations into normal brain cells grown in a cell culture system. Successful identification of the mechanisms will provide a starting point for developing diagnostic and therapeutic strategies for translation to affected patients.