Investigation of synaptic defects in autism using patient-derived induced pluripotent stem cells

Grant Award Details

Investigation of synaptic defects in autism using patient-derived induced pluripotent stem cells

Grant Type: Basic Biology III

Grant Number: RB3-05229

Project Objective: The goal of the project is to establish an in vitro human neuronal model of autism spectrum disorders (ASD) by generating induced pluripotent stem (iPS) cell lines from patients with mutations in Neuroligin (NLGN)or Neurexin (NRXN) genes, differentiating them into forebrain neurons,
and characterizing their synaptic defects at the cellular and molecular level.

Investigator:

Name:	Anirvan Ghosh
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Autism, Neurological Disorders, Pediatrics

Human Stem Cell Use: iPS Cell

Award Value: $843,597

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Investigation of synaptic defects in autism using patient-derived induced pluripotent stem cells

Public Abstract:

Autism spectrum disorders (ASD) are a group of neurodevelopmental diseases that occur in as many as 1 in 150 children in the United States. Three hallmarks of autism are dysfunctional communication, impaired social interaction, and restricted and repetitive interests and activities. Even though no single genetic defect has been ascribed to having a causative role in the majority of ASD cases, twin concordance studies and rare familial forms of the disease strongly support a genetic malfunction and a combinatorial effect of genetic risk factors may contribute to the variability in the symptoms. One major obstacle to ASD research is the difficulty in obtaining human neural tissue to model the disease in vitro. Mouse models of ASD are limited since only rare genetic mutations have been identified so far, and single mutations in those genes cannot fully reproduce the range of critical behaviors characteristic of ASD. Direct reprogramming of patient tissues to induced pluripotent stem (iPS) cells and derivation of forebrain neurons from them will provide much needed insight into the molecular mechanism of neuronal dysfunction in diverse individuals on the autism spectrum. The use of patient-derived stem cells to characterize cellular defects brings together two investigative approaches. One is the identification of common cellular and molecular mechanisms that are central to deficiencies across diverse populations of patients. The other is quantitative comparison of pathological features that address differences amongst diverse patients. Our major goal is to characterize the synaptic dysfunction using concrete, quantifiable parameters in human neurons that have specific mutations in key synaptic proteins. This approach will give us a handle into the molecular synaptic complexes that may also be altered in sporadic ASD cases and could help us develop drug strategies that can normalize synaptic function. Although several groups are interested in generating iPS cells from autistic patients, these efforts generally do not have genomic information on the patients, and the large diversity of mutations associated with autism could lead to large variation in synaptic phenotypes. By focusing on generating iPS cells from patients carrying mutations in a small number of critical synaptic proteins and characterizing the molecular components of this complex, we are likely to be in a strong position to identify novel molecular defects associated with autistic synapses. Relative biochemical comparisons of wildtype and mutant protein complexes could help us find ways to restore synaptic function in ASD.

Statement of Benefit to California:

Many children in California are affected by autism spectrum disorders, which include monogenic syndromes such as Fragile X syndrome and Rett syndrome. However, the majority of cases are idiopathic and an interplay of multiple genetic risk factors is suspected. Since no current drug therapies exist for autism and an accurate diagnosis can only be made in early childhood by largely behavioral criteria, the cost of care and social burden for such a disorder is high, not to mention the devastation to the quality of life for the families of affected children. We would like to identify a core set of proteins found in synapses that are disrupted or dysregulated in autism by a biochemical approach. If we succeed in this effort, we may be able to identify novel biomarkers and molecular targets for specific patient profiles, and by cross-correlating the genetic background to specific behavioral traits in specific individuals, we may come up with molecular targets that are able to address particular symptoms, which should greatly aid in therapeutic regimens that complement existing behavioral therapies. Generating iPS neurons with known copy number variations associated with autism would be a major resource for other laboratories in California and in the field in general. The economic benefit to California is manifold, as many pharmaceutical and biotech companies in California will want to exploit these novel cell lines and the therapeutic targets identified through them in order to design better drugs for autism.

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