Reporting Period: Year 1

Autism Spectrum Disorders (ASD) have a worldwide prevalence of 1% (>1.5 million in the US) and a lifetime cost per affected individual of $3.2M. ASDs are amongst the most heritable of psychiatric disorders. Genome Wide Association studies utilizing samples in the thousands provide only weak evidence for common allele risk effects; positive findings rarely replicate, and genetic effects sizes are small (odds ratios of ~1.1). In contrast, evidence to date for risk or causation conferred by rare variation, particularly rare copy number variants, is very strong. Pathway analyses of the rare mutations implicated and genome-wide transcriptome analysis of brain and blood tissue provide converging evidence that neural-related pathways are central to the development of autism. Core impairments of ASDs, such as imagination and curiosity about the environment, cannot be modeled well in other organisms. The mechanisms underlying ASDs need to be studied in humans and cells that share the genetic background of the patients, such as neurons from patients derived from induced pluripotent cell lines (iPSC). Our goal was to provide the CIRM repository with samples from 200 well characterized individuals with an ASD and 100 demographically matched controls. To date we have enrolled 63 participants.

Reporting Period: Year 2

The goal of the project is to recruit 200 individuals with an autism spectrum disorder (ASD) and 100 demographically matched controls for derivation of induced pluripotent stem cells (iPSCs). The cells will be deposited in a biorepository and made available to other researchers upon request. ASDs have a worldwide prevalence of 1% (>1.5 million in the US) and a lifetime cost per affected individual of $3.2M. ASDs are amongst the most heritable of psychiatric disorders. Genome Wide Association studies utilizing samples in the thousands provide only weak evidence for common allele risk effects; positive findings rarely replicate, and genetic effects sizes are small (odds ratios of ~1.1). In contrast, evidence to date for risk or causation conferred by rare variation, particularly rare copy number variants, is very strong. Pathway analyses of the rare mutations implicated and genome-wide transcriptome analysis of brain and blood tissue provide converging evidence that neural-related pathways are central to the development of autism. Core impairments of ASDs, such as imagination and curiosity about the environment, cannot be modeled well in other organisms. The mechanisms underlying ASDs need to be studied in humans and cells that share the genetic background of the patients, such as neurons from patients derived from induced pluripotent cell lines (iPSC). Recruitment of participants occurred through the Autism and Developmental Disabilities Clinic (ADDC) at Stanford University, direct referrals to investigators, through the Stanford autism research registry, from completed and ongoing research studies, and through advertisement on the web and print. To date we have recruited 181 subjects of the 300 total.

Reporting Period: NCE Year 3

Our original target was to recruit 300 ASD subjects and controls for derivation of induced pluripotent stem cells. The cells will be deposited in a biorepository and made available to other researchers upon request. ASDs have a worldwide prevalence of 1% (>1.5 million in the US) and a lifetime cost per affected individual of $3.2M. ASDs are amongst the most heritable of psychiatric disorders. Genome Wide Association studies utilizing samples in the thousands provide only weak evidence for common allele risk effects; positive findings rarely replicate, and genetic effects sizes are small (odds ratios of ~1.1). In contrast, evidence to date for risk or causation conferred by rare variation, particularly rare copy number variants, is very strong. Pathway analyses of the rare mutations implicated and genome-wide transcriptome analysis of brain and blood tissue provide converging evidence that neural-related pathways are central to the development of autism. Core impairments of ASDs, such as imagination and curiosity about the environment, cannot be modeled well in other organisms. The mechanisms underlying ASDs need to be studied in humans and cells that share the genetic background of the patients, such as neurons from patients derived from induced pluripotent cell lines (iPSC). Recruitment of participants occurred through the Autism and Developmental Disabilities Clinic (ADDC) at Stanford University, direct referrals to investigators, through the Stanford autism research registry, from completed and ongoing research studies, and
through advertisement on the web and print. Due to our success in obtaining these samples we were asked by CIRM to recruit additional samples of Phelan McDermid Syndrome (PMS), and Major Depressive Disorder (MDD). As a result, blood or skin samples have been collected from a total of 420 subjects: 301 ASD, 53 PMS, and 66 MDD. Details for each disorder are presented below.

Induced pluripotent stem cells from children with autism spectrum disorders

**Grant Type:** Tissue Collection for Disease Modeling

**Grant Number:** IT1-06571

**Project Objective:** The project objective is to collect biological samples and information from children with Autism for generation of iPSCs as part of the CIRM iPSC initiative.

**Investigator:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Joachim Hallmayer</th>
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<tbody>
<tr>
<td>Institution</td>
<td>Stanford University</td>
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<td>Type</td>
<td>PI</td>
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**Disease Focus:** Autism, Neurological Disorders, Pediatrics

**Award Value:** $530,265

**Status:** Closed

**Application Title:** Induced pluripotent stem cells from children with autism spectrum disorders

**Public Abstract:** Autism spectrum disorders (ASD) are a family of disabling disorders of the developing brain that affect about 1% of the population. Studying the biology of these conditions has been difficult as they have been challenging to represent in animal models. The core symptoms of ASD, including deficits in social communication, imagination and curiosity are intrinsically human and difficult to model in organisms commonly studied in the laboratory. Ideally, the mechanisms underlying ASDs need to be studied in human patients and in their cells. Since they maintain the genetic profile of an individual, studying neurons derived from human induced pluripotent stem cells (hiPSC) is attractive as a method for studying neurons from ASD patients. hiPSC based studies of ASDs hold promise to uncover deficits in cellular development and function, to evaluate susceptibility to environmental insults, and for screening of novel therapeutics. In this project our goal is to contribute blood and skin samples for hiPSC research from 200 children with an ASD and 100 control subjects to the CIRM repository. To maximize the value of the collected tissue, all subjects will have undergone comprehensive clinical evaluation of their ASD. The cells collected through this project will be made available to the wider research community and should result in a resource that will enable research on hiPSC-derived neurons on a scale and depth that is unmatched anywhere else in the world.
Statement of Benefit to California:

The prevalence and impact of Autism Spectrum Disorders (ASD) in California is staggering. California has experienced 13% new ASD cases each year since 2002. ASD are a highly heritable family of complex neurodevelopmental conditions affecting the brain, with core symptoms of impaired social skills, language, behavior and intellectual abilities. The majority with an ASD experience lifelong disability that requires intensive parental, school, and social support. The result has been a 12-fold increase in the number of people receiving ASD services in California since 1987, with over 50,000 people with ASDs served by developmental and regional centers. Within the school system, the number of special education students with ASD in California has more than tripled between 2002 and 2010. The economic, social and psychological toll is enormous.

It is critical to both prevent and develop effective treatments for ASD. While rare genetic mutations account for a minority of cases, our understanding of idiopathic ASD (>85% of cases) is extremely limited. Mechanisms underlying ASDs need to be studied in human patients and in cells that share the genetic background of these patients. Since they maintain the complete genetic background of an individual, hiPSCs represent a very practical and direct method for investigating neurons from ASD patients to uncover cellular deficits in their development and function, and for screening of novel therapeutics.

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