COLUMBIA UNIVERSITY
MEDICAL CENTER

JORDAN'S
GUARDIAN ANGELS

SEATTLE Children's
HOSPITAL · RESEARCH · FOUNDATION

PPP2R5D Gene Research "Jordan's Syndrome"

Executive Summary

Problem

Recent research studies* have identified several variances (mutations) occurring in the gene PPP2R5D that are related to or causing a host of neurodevelopmental disorders in the human brain. These disorders include Intellectual Disability (ID), some forms of Autism Spectrum Disorder and associated physical conditions. In addition, the identified mutations are also linked to Alzheimer's Disease and certain forms of cancer.

Research Proposal

The identification of these mutations and their impacts presents an opportunity to conduct foundational research aimed at developing therapeutical treatments or possibly reversing the impacts of the mutations. The research proposed in the attached prospectus includes the following basic elements:

1. Identification of additional patients impacted by the mutations. Currently, we have identified 69 children who are affected by the various mutations of PPP2R5D. As Whole Exome Sequencing (WES) becomes more available as a diagnostic tool we expect that our sample size for the research will increase significantly, with a goal of 100 patients ultimately involved in the research study efforts.
2. Pluripotential brain Stem Cells. The research plan includes the creation of Pluripotential brain stem cells through the collection of cell and blood samples from the identified patients. These cell samples will allow for a detailed observation of the mutations and their characteristics.
3. Creation of Mouse Models. The research plan also includes creation of mouse models that have the corresponding genetic mutations. This will allow direct examination of the mouse brain and performance of invasive studies that are not possible in human patients.
4. High Throughput Drug Screening. After creation of the two samples above, high throughput drug screening will be performed to determine those drugs that are effective at either treating or reversing the mutations and testing for toxicity of the drugs on the samples.
5. Creation of 3D structure of the protein. The 3D model helps explain the effect of the different mutations on the individuals and enables the development of a targeted drug.

Other Research Benefits

Although we are studying these mutations specifically for their impact on Intellectual Disability as well as Autism Spectrum Disorder, there are other possible byproducts that may be derived from this research. As mentioned above those include potential impacts on the study of Alzheimer's Disease as well as cancer.

*De Novo missense variants in PPP2R5D are associated with intellectual disability, macrocephaly, hypotonia, and autism. Published in Neurogenetics October 22nd 2015

Research Goals

The goals of this foundational research are the following:

1. To develop therapeutic treatments for the neurological disorders, caused by the mutations, including ID and ASD
2. Potential ability to reverse the mutations and eliminate their impacts on both ID and ASD as well as exploring the mutations impacts on Alzheimer's disease and certain cancers.
3. Create the information to allow for potential gene editing to eliminate the mutations.
4. It is anticipated that within 3-5 years the research will result in therapeutic treatments or a mechanism to reverse the mutations for the purpose of undergoing human clinical trials.

Research Budget

Below is a preliminary budget for the various research elements and activities, indicating a preliminary budget of approximately $10 million.

Function	Budget
Clinical registry and biorepository	1,000,000
Phosphoprotein characterization	$400,000
Biochemical studies	$400,000
Structural protein characterization	$250,000
iPSC generation and differentiation and characterization	$300,000
High throughput drug screening in vitro	$2,000,000
Mouse model generation and characterization	$1,250,000
Mouse clinical trials	$3,000,000

Attached is a schematic diagram providing more detailed steps of the research.
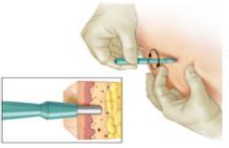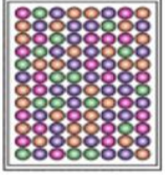
collect human cells

iPSCs

Neurons

define aberrant protein phosphorylation

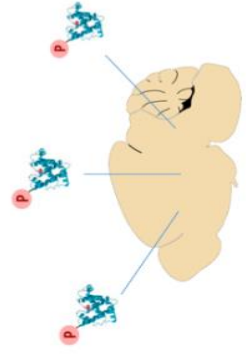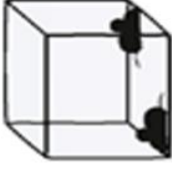define a cellular phenotype

high throughput drug screen

test lead compound in animal models and test for efficacy and toxicity
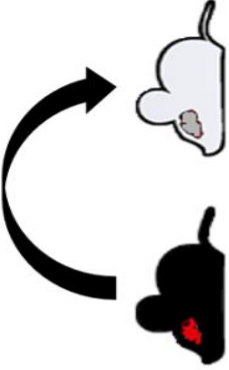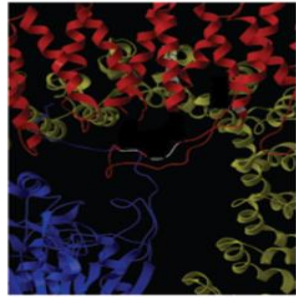
Create mouse models

characterize the brain and behavior and how these develop
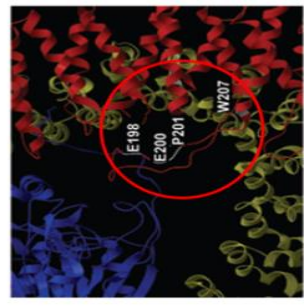
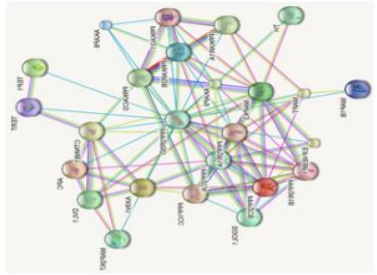define aberrant protein phosphorylation in different brain regions

Test for reversibility

3-D protein structure

determine the location of the 4 mutations and the change in protein conformation with the mutations

map protein-protein interactions

E198
E200
P201
W207