Research Focus Areas:

CACNA1A: This RFA aims to advance the discovery or development of therapeutic treatments and/or cures for CACNA1A-related diseases. These are rare autosomal dominant neurodevelopmental disorders caused by a mutation in the CACNA1A gene, which encodes for the pore-forming alpha 1A subunit of the voltage-gated calcium ion channel Cav2.1. This channel plays a major role in fast synaptic neurotransmitter release in the brain. The spectrum of neurological phenotypes associated with CACNA1A variants includes hemiplegic migraine (sporadic and FHM1), episodic ataxia type 2 (EA2), epileptic encephalopathies, global developmental delays, intellectual disability, ASD, hypotonia, eye movement disorders, cerebellar atrophy, and neuropsychiatric disorders.

We seek applications for **one $73,731 grant** that will strongly impact the CACNA1A community. Specific areas of interest include:

- Discovery and validation of biomarkers (molecular and functional). To date, no CACNA1A-specific biomarkers have been identified.
- Novel therapeutic approaches for CACNA1A-related disorders. The heterogeneity of symptoms requires the development of multiple therapeutic treatments for the CACNA1A community. Approaches we are interested in funding include (but are not limited to): drug repurposing, small molecules, gene therapies, and RNA-based therapies. While we are looking for approaches that will broadly impact the patient community, we will also support the development of disorder-specific treatments.
- Identification of disease mechanisms. Developing specific treatments highly depends on understanding how variants impact protein function and lead to disease phenotypes. There are over 300 unique pathogenic CACNA1A variants reported in Clinvar, with little molecular data. We are interested in funding work that expands the study of disease mechanisms among CACNA1A variants to accelerate therapeutic development.
- Variant Classification. In addition to functional characterization of variants, there is a need for a more comprehensive method of classifying CACNA1A variants. We seek someone with expertise in designing a universal and systematic method for variant classification and identifying diverse but relevant criteria for incorporating data from sources including computational predictive models, cellular electrophysiology, and animal models, especially for a calcium ion channelopathy.

In addition, applicants are encouraged to collaborate with existing CACNA1A researchers and to leverage existing disease models and data (animal models, patient-derived cell models in our CombinedBrain biobank, CACNA1A Natural History Study, Ciitizen data, etc.) This grant is made possible by Team CACNA1A and the CACNA1A Foundation.