TITLE: High-resolution imaging to measure expanded microsatellite repeats in neurological disease

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RESEARCH PROJECT DESCRIPTION

Microsatellite repeat expansions cause >30 inherited neuromuscular and neurological diseases, including myotonic dystrophy, ALS, Huntington's Disease, and Spinocerebellar Ataxias. Expanded nucleotide sequences of 3-6 nucleotides in these diseases can cause cellular toxicity through RNA gain of function, as well as protein gain-of-function. Generally, longer repeats correlate with earlier age of onset and more severe disease symptoms. A unique feature of these DNA mutations is that the length of the repeat tract is unstable – it can change across generations of an affected family (intergenerational instability), as well as across different cells in within a single affected tissue (somatic instability). While it is straightforward to assay whether an individual has expanded alleles, it is extremely challenging and laborious to obtain an accurate measurement of the full repeat length distribution in an individual. Being able to obtain this measurement would significantly accelerate our ability to understand and treat these diseases. For example, we would be able to better classify individuals in a clinical trial. In addition, if we could control for underlying repeat lengths across individuals, we could better search for genetic modifiers that may protect or enhance disease phenotypes.

We are developing a new high-resolution, image-based approach to measure expanded repeat length tracts. In this project, the student would isolate genomic DNA samples from human blood, tissue, and cell lines, and prepare them for this approach. Techniques would include molecular biology to fluorescently label specific DNA loci, construction of imaging flow-cells, high-resolution microscopy, and development of computational approaches to analyze images.