CALIFORNIA STATE SCIENCE FAIR
2013 PROJECT SUMMARY

Name(s)

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Project Number

S1215

Project Title

Evaluating the Prevalence of Noncoding Repeat Expansions in Amyotrophic Lateral Sclerosis

Abstract

Objectives/Goals

Though no treatments for amyotrophic lateral sclerosis (ALS) currently exist, evidence suggests that the disease is strongly rooted in genetic origins. Recently, expansions of CAG (glutamine coding) repeats in several genes, including NIPA1, ataxin 2, and c9orf72, have been linked to ALS incidence, raising the possibility of a broad role for repeat expansions in ALS susceptibility. Repeat expansions in c9orf72, the most common abnormality linked to ALS as of yet, are in a noncoding region of the gene. The likely mechanism of action of these noncoding repeat expansions occurs via accumulation of toxic RNA foci, resulting in sequestration of various RNA binding proteins and general disruption of the transcriptome. I chose to investigate six candidate genes previously linked to neuromuscular disorders - NOP56, JPH3, DMPK, ATXN8, PPP2R2B, and ATXN10 - for a possible link between noncoding repeat expansions in the genes and ALS susceptibility.

Methods/Materials

Polymerase chain reaction, gel electrophoresis, and capillary electrophoresis were used to amplify and determine the repeat lengths of the genes of interest in 730 ALS patients and 700 control patients. In addition, this study presents an automated technique, developed in Java, of inferring allelic repeat number from fragment analysis data. This method has been successfully applied to analyze more than 4,000 individual data points for genotyping and can also be utilized for other applications of electropherograms, which are used widely in molecular biology.

Results

Receiver operating characteristic analysis and Fisher#s exact test revealed a significant association between ataxin 8 repeat length and ALS. Ongoing and future work includes investigating other genes for associations with ALS, refining and expanding the automated electropherogram analysis, as well as utilizing TALENs to induce these repeat expansion mutations in cell culture models in order to test the RNA foci hypothesis.

Conclusions/Discussion

This study has both identified a novel gene candidate associated with amyotrophic lateral sclerosis incidence and introduced a new technique of automating fragment analysis based genotyping. These findings can prove instructive in characterizing the genetic interactions which lead to ALS, paving the way for potential diagnostic methods such as genetic screening to identify ALS as early as possible.

Summary Statement

This study has both identified a novel gene candidate associated with amyotrophic lateral sclerosis incidence and introduced a new technique of automating fragment analysis based genotyping.

Help Received

Research performed during internship at the Gitler Lab at Stanford University