CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP110054

Project Title:
Genetic Analysis of Anticipation in Lynch Syndrome

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Lynch syndrome (LS) is a genetic disorder that is caused by a mutation in one of four genes that repair genetic material when it becomes damaged (mismatch repair genes). People who inherit mutations in these genes are predisposed to the development of a variety of cancers with colon and endometrial cancer being the most common. This predisposition is due to instability in the genome. The goal of this study is to try to understand why, in families carrying these mutations, LS patients tend to develop cancer earlier in life with successive generations. We have previously found that low levels of genetic instability can be detected in DNA isolated from blood cells of LS patients. This suggests that DNA repair is not carried out efficiently in constitutive (i.e.non-tumor) tissue. We hypothesize that due to these low levels of genome instability, de novo or new spontaneous mutations occur in the germ cells of LS patients, which are passed on to their offspring. Some of these mutations may convey an increased risk for developing cancer earlier in life. We propose to sequence DNA from family quartets of LS families consisting of the LS parent, non-LS spouse, LS offspring and non-LS offspring and compare to control quartets to determine if there is a higher level of de novo mutations in the offspring of LS parents compared to normal controls and to determine if the mutational load is associated with the anticipation observed in these families. The proposed studies will allow an unparalleled characterization of the de novo germline mutations in LS. Understanding the mechanisms for anticipation in LS and the ability to identify genes that display de novo mutations in LS would provide an important tool for predicting which LS patients will develop cancer at an earlier age. As next generation technology continues to become more affordable, genome sequencing may eventually become a clinical test to identify LS offspring who are more likely to develop cancer earlier in life.