CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180751

Project Title:
Methods for Assessment and Quantification of Imperfect dsDNA Break Repair

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Defective DNA repair may be inherited and so could be present in every cell of the body. Alternatively, it may appear at some point during tumorigenesis and thus be restricted to only a subset of cells. In both cases, such defects will result in elevated mutation levels. These mutations will follow patterns which are shaped by the specific DNA repair pathway that has been affected, the stage of tumorigenesis, and also by tissue-specific and environmental factors. There is an ongoing effort to identify and classify a category of these mutations known as clonal mutations, which are amplified in specific tissues, for instance by cancer growth. However, current sequencing methods are not sensitive enough to detect mutations before they are clonally amplified.

Many cancer patients have defects in DNA repair that result in deletions of short fragments of their DNA. These deletions happen randomly, do not repeat between cells, and appear in both healthy and cancerous cells. However, if one considers all those rare deletion events together, their level is higher than in a person without DNA repair defects. We hypothesize that the number of these deletions, combined with other features of the deletions' presence, may serve as a biomarker in cancer diagnosis and treatment. To this end, we propose to develop and implement a method that would use whole genome sequencing data to quantify deletion levels, classify them into those originating from defects in DNA repair and those resulting from other processes, and then correlate the levels of those deletions with other cancer and environmental characteristics.

Having a method to measure the level of such deletions before a cancer is established would also provide a direct assessment of the functional impact of variants of unknown significance (VUS), and so would guide preventive strategies, would contribute to early diagnosis, and would help to design and select personalized treatments.