

Poster 24: Characterization of genomic and social determinants of health in the TP53 mutational landscape of non-cancerous endometrium during the lifespan of Black and White individuals

Eric Rios-Doria, MD – University of Washington

Topic: Endometrial

Objectives

Characterize TP53 mutations in benign endometrium acquired throughout a woman's lifespan with integration of social determinants of health.

Methods

Endometrial tissue was collected at autopsy, confirmed with H&E staining, and macrodissected. Ultra-deep duplex sequencing (~5,000x) of isolated DNA was used to sequence TP53 somatic mutations with high resolution. Each individual's TP53 mutation frequency was calculated as the total TP53 variant reads divided by the total duplex nucleotides sequenced. Socioeconomic metrics were acquired using zip codes and the 2021 US Census Bureau American Community Survey. Individuals with a history of endometriosis, prior malignancy, or prior chemotherapy were excluded.

Results

Benign endometrial tissue was collected from the autopsies of 39 individuals (13 Black, 26 White); with 12 samples aged 0-19 years, 14 aged 20-39 years, 7 aged 40-59 years, and 5 aged over 60 years. 165 TP53 mutations were identified (Figure 1). Variant types included 67% missense (n=110), 14% insertion-deletion (n=23), 10% synonymous (n=17), 5% nonsense (n=9), and 4% splice (n=6). 66% (73/110) of missense mutations were found in the DNA binding domains of the TP53 protein. TP53 mutation frequency increased linearly with age amongst the entire cohort (Spearman correlation p< 0.01). 13% of all mutations were identified in more than one duplex mutant read (large clone) beginning at age 18 through age 81. Most socioeconomic data indicated a more wealthy and educated sample compared to national medians, however there was significant variability among individuals. There was no statistical association between socioeconomic metrics and mutational burden of Black and White individuals.

Conclusions

The burden of somatic TP53 mutations in benign endometrium is associated with older age. Most somatic mutations identified were pathogenic, either loss-of-function variants or missense mutations affecting the DNA binding domain and impacting function. TP53 clonal expansions exponentially increased in the second decade of life, which could suggest a relationship to hormonal changes, a hypothesis warranting future study. Additional data are needed to determine the role of socioeconomic factors in TP53 genomic burden.

Abstract Table or Graph SPAZFWFX-1515559-1-ANY.pdf