Tumor only analysis of whole exome sequencing from a multi-institutional Nigerian prostate cancer cohort reveals DNA repair genes associated with African ancestry

Jason A. White; Ernest Kaninjing; Kayode A. Adeniji; Paul Jibrin; John O. Obafunwa; Chidiebere N. Ogo; Mohammed Faruk; Solomon Rotimi; Ademola Popoola; Omolara A. Fatiregun; Olabode P. Oluwole; Balasubramanyam Karanam; Wei Tang; Stefan Ambs; Folake T. Odedina; Damali N. Martin; Clayton Yates

Abstract

Men of African ancestry (MAA) have the highest global incidence and mortality of prostate cancer (PCa); however, the biology underlying this harsh disease presentation remains poorly understand, largely due to Africans and people within the African diaspora being under-represented in genomics research. MAA are younger at diagnosis, have higher tumor volume at diagnosis and have higher tumor aggression compared to European American men. Additionally, genomic profiling continues to show that PCa etiology and phenotype are influenced by higher amounts of African ancestry and that West African ancestry is associated with unique genomic alterations. Herein we utilize whole exome sequencing of a unique cohort of 45 advanced stage, treatment naïve Nigerian primary PCa tumors and 11 unmatched non-tumor tissue to compare genomic variants with African (AA) and European (EA) American TCGA PCa tumors. Nigerian samples were collected from 6 sites in central and southwest Nigeria. After whole exome sequencing, samples were processed using GATK best practices. Four genes [BRCA1 (100%), BARD1 (45%), BRCA2 (27%) and PMS2 (18%)] had germline variants in at least two Nigerian non-tumor samples. Across 111 germline variants, the AA cohort reflected a pattern [BRCA1 (68%), BARD1 (34%), BRCA2 (28%) and PMS2 (16%)] similar to Nigerian samples. Of the most frequently mutated genes, BRCA1 showed a statistically ($p \leq 0.05$) higher mutation frequency in MAA. Disaggregating gene level mutation frequencies by variant revealed both ancestry linked and Nigerian specific germline variant patterns. Driven by rs799917, BRCA1 showed increasing mutation frequency as African admixture increased. BRCA2_rs11571831 was only present in MAA and BRCA2_rs766173 was increased in Nigerian men. 133 somatic variants were present in 26 PCa associated genes within the Nigerian tumor cohort. Nine genes [BRCA2 (27%), APC (20%), ATM (20%), BRCA1 (13%), DNAJC6 (13%), EGFR (13%), MAD1L1 (13%), MLH1 (11%) and PMS2 (11%)] showed mutation frequencies above 10%. Compared to TCGA cohorts, BRCA2, APC and BRCA1 showed statistically significant increases in Nigerian tumors. The Nigerian cohort variant pattern shared similarities (cosign similarities ≥ 0.734) with COSMIC signatures 5 and 6 and mutated genes showed significant ($q < 0.001$) GO and functional enrichment in mismatch repair and non-homologous repair deficiency (HRD) pathways. Here, we show that variants in DDR genes are increased in Nigerian PCa and that a portion of those variants correlate with increased African ancestry. Moreover, we identify variants of unknown significance that may contribute to population specific routes of tumorigenesis and treatment. These results present the most comprehensive characterization

of the Nigerian PCa exome to date and further highlight the need to increase study population diversity.