LETTER

Next-generation sequencing in African Americans with colorectal cancer

We read with interest the recent study by Guda et al. (1) on novel recurrently mutated genes in African Americans with colorectal cancer (CRC). We have also recently published a similar study on African Americans from the Washington, DC area in which we reported novel mutations within known cancer pathways (2).

Guda et al.'s paper provides evidence that a set of novel genes seems to be preferentially mutated in African Americans with CRC. They specifically discussed ephrin type A receptor 6 (*EPHA6*) and folliculin (*FLCN*), the top genes in their 20 genes' panel, identified in microsatellite-stable (MSS) and low-mutation rate CRC tumors. Their approach was primarily focused on detecting genes with differential mutation rates between African Americans and Caucasians.

Our approach's focus was to look for differential mutations within known cancer pathways, which led to a definition of new mutations within the adenomatous polyposis coil (*APC*) gene as well as within MSH3 and MSH6 DNA MMR genes that are not usually considered as primary targets in colon carcinogenesis.

There are limited next-generation sequencing studies in African Americans with cancer in general and with CRC in particular, which remains high among African Americans (3). As such, it is a challenging task to predict the frequency and incidence of any mutation, be it in novel or in well-known cancer genes. Both of our studies combined account for only 41 whole-exome–sequenced African American CRC tumors. Therefore, more exome studies are needed in minority patients to have a meaningful evaluation of mutations' weight within such populations and to also assess cohorts' variations in the context of CRC disease and disparity, nationwide.

We checked Guda et al.'s newly identified genes and mutations in our cohort. There are seven somatic protein-changing mutations common between the two cohorts. These mutations are in five genes, notably *APC* and *KRAS*. These mutations are spread across 6 of 11 of our MSS samples and 12 of 29 samples in Guda et al.'s dataset. Of their 20 genes' panel, our samples have nine somatic protein-changing mutations in six genes (notably *WDR87*), but none in their two top genes: *EPHA6* and *FLCN*. That result is not surprising considering the fact that the overall mutation frequency of the two genes in their dataset is low (5.83% and 2.91%, respectively). Considering all mutations, our samples have 459 mutations in 18 of the 20 genes with *WDR87*, again the gene with the highest number of mutations.

The analysis of Guda et al.'s 20 genes in our cohort gives more credibility to their findings as to the potential race-specific nature of these target genes. If complemented with our approach of looking for novel, highly pathogenic mutations within known cancer genes and pathways, the outcome would likely allow a better definition and understanding of race-specific cancer genes and mutations. Large nationwide studies are needed to reach that goal.

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1 Guda K, et al. (2015) Novel recurrently mutated genes in African American colon cancers. *Proc Natl Acad Sci USA* 112(4): 1149–1154.

2 Ashktorab H, et al. (2015) Identification of novel mutations by exome sequencing in African American colorectal cancer patients. *Cancer* 121(1):34–42.

3 American Cancer Society (2011) *Colorectal Cancer Facts and Figures 2011–2013* (American Cancer Society, Atlanta).

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The authors declare no conflict of interest.

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