WHOLE EXOME SEQUENCING OF INDIVIDUALS PRESENTING EXTREME PHENOTYPES OF HIGH AND LOW-RISK OF DEVELOPING TOBACCO-INDUCED LUNG ADENOCARCINOMA: RELEVANCE OF IMMUNE AND DNA-REPAIR RELATED PATHWAYS

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Abstract

Background Individual susceptibility to carcinogens may depend on genetic background. We performed for the first-time Whole Exome Sequencing (WES) of germline DNA from individuals presenting phenotypes of extreme sensitivity and resistance to developing tobacco-induced lung adenocarcinoma, in order to characterize the genetic background associated with these relevant phenotypes.

Methods We performed WES of germline DNA from heavy smokers (≥15 pack-years) who either developed lung adenocarcinoma at an early age (≤55 years, extreme cases, n=50) or did not present lung adenocarcinoma or other tumors at an advanced age (≥72 years, extreme controls, n=50). We selected non-synonymous variants (missense and non-sense) located in the coding regions and consensus splice sites of the genes showing significantly different allelic frequencies between both cohorts. We validated our results in germline data from 52 additional extreme cases selected from TCGA using the same criteria (diagnosis of lung adenocarcinoma at ≤55 years, tobacco consumption ≥15 pack-years).

Results The mean age for the extreme cases and controls was respectively 49.7 and 77.5 years. Mean tobacco consumption was 43.5 and 54.4 pack-years. We identified 619 significantly different variants between both cohorts, and we validated 107 of these in 52 extreme cases selected from TCGA (mean age 49.3 years, mean tobacco consumption 37 pack-years). Nine validated variants, located in relevant cancer related genes, such as PARP4 (DNA repair), HLA-A (antigen presentation) or NQO1 (detoxification) among others, achieved statistical significance in the False Discovery Rate test (FDR) (table 1). The most significant validated variant (p=4.48 × 10−5) was located in the tumor-suppressor gene ALPK2. The Reactome Pathway Database analysis showed that the genes harboring the most significant validated variants were significantly related to antigen processing and presentation, interferon and cytokine signaling and immune regulation, also achieving statistical significance in the FDR test (table 2).

Conclusions We describe for the first time genetic variants associated with extreme phenotypes of high and low-risk for the development of tobacco-induced lung adenocarcinoma, assessed with WES. The most significant validated variants were related with antigen presentation, immune regulation and DNA repair. Our results and our strategy warrant further development to characterize these clinically relevant phenotypes.

Ethics Approval The study was approved by the Investigational Review Board of Clinica Universidad de Navarra, approval number 021/2009.

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Routine Use of Comprehensive Genomic Profiling to Assess Tumor Mutational Burden Across a Community Health System

Background Tumor mutational burden (TMB), defined as the average number of somatic mutations per megabase (mut/Mb) of DNA in tumor cells, has emerged as a predictive biomarker for response to immune checkpoint inhibitor (ICI) therapy. With more widespread adoption of comprehensive genomic profiling (CGP) assays in the clinic, it is now possible to routinely assess TMB across a wide variety of advanced cancers. Here we performed a retrospective study of routine TMB results assessed from CGP testing across a large community health system to reveal novel insights into the proportion of patients that may benefit from ICI treatment.

Methods Patients in the Providence Sr. Joseph Healthcare system diagnosed with advanced or metastatic solid tumors and tested for TMB using CGP tests (TruSight Oncology 500, research use only) between July 2019 and July 2020 were considered in this study. Deidentified electronic medical record data and CGP results were abstracted for downstream study.

Results A total of 1300 patients had one or more CGP tests with a TMB calculation. The median age of patients was 66 years, 51% were female, and 59% were white. TMB values ranged from 0–536 mutations per mut/Mb. Across tumor types, the proportion of patients with TMB ≥10 mut/Mb was 26% (n=341) and with TMB 5–9 mut/Mb was 27% (n=353). The proportion of patients with TMB ≥10 mut/Mb varied by tumor type: Melanoma (60%), NSCLC (42%), CRC (24%), pancreatic (5%). Of all the TMB-tested patients, 90 (7%) received IO therapy post testing. IO therapy use was highest among patients with TMB ≥10 mut/Mb (12%), followed by 7% with TMB 5–9 mut/Mb, and 4% with TMB of 0–5 mut/Mb. Twenty-nine percent of patients with TMB ≥10 also had high PD-L1 expression by IHC as compared to 8% of TMB ≤10. ICI therapy choice in this retrospective cohort appeared to be largely driven by other considerations (PD-L1 immuno-histochemistry etc.) independent of TMB.

Conclusions A minority of TMB ≥10 patients assessed in this study received an ICI therapy, a result that is likely reflective of the lack of definitive guidelines for this emerging biomarker. As the adoption of TMB increases as a biomarker of...