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Characterization of the Genomic and Immune Landscapes of 88 Cases of Pheochromocytomas and Paragangliomas: Implications for Development of Targeted Therapeutics

Udhayvir Singh Grewal[1], Nishant Gandhi[2], Heloisa Soares[3], Michael J. Demeure[4], Jaydira del Rivero[5], Chandrikha Chandrasekharan[1], Joanne Xiu[2], Emil Lou[4].

[1]University of Iowa Holden Comprehensive Cancer Center, Iowa City, IA; [2]Caris Life Sciences, Phoenix, AZ; [3]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [4]Hoag Memorial Hospital Presbyterian and Translational Genomics Research Institute, Newport Beach, CA; [5]National Cancer Institute, Bethesda, MD; [6]University of Minnesota Masonic Cancer Center, Minneapolis, MN.

BACKGROUND

Pheochromocytomas and paragangliomas (PCC/PGL) are rare neuroendocrine neoplasms (NENs) arising from the neural crest tissue. Evolution in the understanding of the biology of these tumors has revealed distinct molecular subtypes with therapeutic and prognostic implications. Due to the rarity of PCC/PGL, however, large-scale studies that integrate the transcriptomic and genomic data with the immune landscape are lacking. Herein, we identified the genomic and immune landscape of PCC/PGL and draw a comparison with other NENs.

METHODS

NENs (non-PCC/PGL: n=4105) and PCC/PGL (n=88) that underwent molecular profiling at Caris Life Sciences (Phoenix, AZ) were included. Tumor microenvironment (TME) composition was estimated using the quanTIseq method on bulk RNA sequencing data. Fishers Exact and Chi-squared tests were used to ascertain statistical significance with the Benjamini–Hochberg method used to correct for multiple comparisons ($q < 0.05$).

RESULTS

Among PCC/PGL, the most common genetic alterations were succinate dehydrogenase subunit B (SDHB) mutations (22.1%), followed by NF1 (11.8%), ATRX (9.9%), SDHD (6.9%) and RET (4.7%) mutations. We identified potentially targetable mutations (RET, FGFR1 and VHL) in 10.3% of patients (10/88). Of the 40 patients with available transcriptomic data, potentially targetable alterations (RET, CREM, NUMA1 and NTRK fusions) were identified in 4 patients (10%) . PCC/PGL had significantly higher prevalence of SDHB (22.1% vs 0.27%), ATRX (9.9% vs 3.3%) and VHL (2.3% vs 0.4%) mutations, ARID1A deletions (3.5% vs 0.2%) and RET fusions (2.5% vs 0.2%) compared to other NENs (all $q<0.05$). Additionally, we noted a higher prevalence of SMO, CSF1R, PDGFRB, AURKB, SMARCB1, MEN1 and NFKB2 amplifications among PCC/PGL (all $q<0.05$). High tumor mutational burden (>10 mut/Mb) was more prevalent among other NENs compared to PCC/PGL (10.5% vs 1.1%, $q=0.02$). M2 Macrophages (6.6% vs 3.5%) and B-cells (6.5% vs 4.6%) were enriched while neutrophils (0.9% vs 2.9%) and T-regulatory cells (0.9% vs 1.5%) were lower in PCC/PGL compared to other NEN tumors (all $q<0.05$).

CONCLUSIONS

Comprehensive analysis of the genomic and immune landscape of PCC/PGL shows distinct differences from that of other NENs. We also noted distinct molecular and tumor immune cell microenvironment features between PCC/PGL and other NENs. These findings extend our understanding of the biology of PCC/PGL and merit further investigation for potential therapeutic and prognostic implications.

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