Malignant Pheochromocytoma (MP): A Comprehensive Genomic Profiling Study


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ABSTRACT

Background: We use CGP to characterize the genomic alterations (GA) in MP and to enable the search for potential therapy targets.

Methods: From a series of 201,766 consecutive clinical cases, 44 cases of clinically advanced MP underwent CGP using a hybrid-capture based commercial assay to evaluate all classes of GA. Tumor mutation burden (TMB) was determined on 0.83-1.14 Mb of sequenced DNA and reported as mutations/Mb (mut/Mb) and microsatellite instability (MSI) was determined on 114 loci. PO-L1 expression was determined by IHC (Dako CD23 antibody).

Results: All patients had clinically advanced recurrent and/or metastatic disease. 23 patients were females and 21 patients were males. There were 34 (77%) of MP known to have originated in the adrenal gland and 10 (23%) of the MP were sequenced from metastatic site where the exact primary site was unknown. The primary tumor was sequenced for sequencing in 14 (32%) of the MP cases and a non-primary tumor metastatic site (i.e., liver, lung, bone, soft tissue, lymph node, kidney, peritoneal cavity, and chest wall) in 30 (68%) of MP cases. 2.3 GA/tumor. The most frequent un-targetable GA were ATRX (25%), TP53 (21%), SDHB (13%), CTNNB1 (7%), VHL (7%), and CDKN2A/2B, PKR2, NOTCH2 and MEN1 (all 5%). The most frequent potentially targetable GA included RET (9%), NF1 (9%) and FGFR1 (5%). PRDM16 GA were found in 2% of MAP. Germline mutations in known cancer predisposition genes were predicted in 8 (18%) of cases involving SDHB (5 cases) and BRC1, MEN1, and MSH2 (1 case each). The genomic signatures of primary MP were not significantly different from that obtained from sequencing of metastatic site biopsies. 0.0 (5) of MP stained positively for PD-L1 expression. The mean TMB was 2.95 mutation/Mb, the median TMB was 2.4 mutation/Mb, 2 (5%) had TMB ≥ 10 mutations/Mb and 0 (0%) and TMB ≥ 20 mutations/Mb. 0 (0%) of 33 MP evaluated for MSI had a MSI-High status.

Conclusions: Although the GA/tumor is relatively low for MP, CGP can reveal important potential therapy targets including RET, NF1 and FGFR1. MP do not reveal strong potential for immunotherapies with low TMB, absence of MSI-High status and low (2%) PRDM16 mutation frequencies.

RESULTS

• 23 patients were females and 21 patients were males and all (100%) had advanced/metastatic disease
• Primary site was the adrenal gland for 34 (77%) and unknown for 10 (23%)  
  Primary tumor sequenced in 14 (32%) and metastatic site in 30 (68%). No difference in GA based on whether primary site or metastatic site was used for sequencing
• There were 2.3 GA/tumor.
• Most frequent un-targetable GA were ATRX (25%), TP53 (21%), SDHB (13%), CTNNB1 (7%), VHL (7%), and CDKN2A/2B, PKR2, NOTCH2 and MEN1 (all 5%).
• Most frequent potentially targetable GA included RET (9%), NF1 (9%) and FGFR1 (5%).
• PRDM16 GA were found in 2% of MAP.
• Germline mutations in known cancer predisposition genes were predicted in 8 (18%) of cases involving SDHB (5 cases) and BRC1, MEN1, and MSH2 (1 case each).
• Mean TMB was 2.95 mutation/Mb, the median TMB was 2.4 mutation/Mb, 2 (5%) had TMB ≥ 10 mutations/Mb and 0 (0%) and TMB ≥ 20 mutations/Mb.
• No MP evaluated (0/33) for MSI had a MSI-High status.
• No MP (0/5) stained positively for PD-L1 expression.

MATERIALS AND METHODS

• ≥50 ng DNA extracted from 40 µm of FFPE sections
• Sequencing performed for up to 315 cancer-related genes and introns from 28 genes commonly rearranged in cancer
• Hybrid capture-based sequencing using adapting ligation-based libraries
• Mean coverage depth >600X
• Base substitutions, insertions and deletions (short variants; 5V), rearrangements, and copy number changes were assessed
• Tumor mutational burden (TMB) calculated from 0.83-1.14Mb sequenced DNA

CONCLUSIONS

• MP represent a rare form of endocrine cancer that feature a variety of genomic alterations
• Although the GA/tumor is relatively low for MP, CGP can reveal important potential targets for therapy in the metastatic setting including RET, NF1 and FGFR1
• MP do not reveal strong potential for immunotherapy with low TMB, absence of MSI-High status and low (2%) PRDM16 mutation frequencies
• Based on this data, further study of CGP as a method of developing precision therapies for MP appears warranted

CASES

Sporadic malignant pheochromocytoma in a 45 year old Caucasian man. Comprehensive genomic profiling of a primary tumor revealed amplification of the RICTOR, CCDC2, FGFR2 and FGFR3 genes along with short variant mutations in EGFR (c.2565_2566dup), PIK3CA (c.546_547insK), and CDKN2A (c.51_52insA) (all 1 case each). RICTOR amplification was found in 14 (2/3 of cases in the Pheochromocytoma and Paraganglioma TCGA dataset and in 7% (2/28) of cases in the Adrenaloma/Paraganglioma TCGA dataset (Gleason, Dec 2014). RICTOR with amplification may be sensitive to Inhibitors of mTORC2. Numerous inhibitors that target both mTORC1 and mTORC2 complexes, as well as dual PI3K/mTOR inhibitors, are under preclinical and clinical investigation in multiple tumor types. Preclinical studies have explored combined mTORC1 and mTORC2 targeting as potential therapeutic strategy against pheochromocytomas.