BAP1 Tumor Predisposition Syndrome: Preliminary data from a laboratory-based multi-gene panel testing cohort

Background: Germline mutations in BAP1 have recently been shown to cause a tumor predisposition syndrome characterized by renal cell carcinoma (RCC), uveal melanoma, cutaneous melanoma, and mesothelioma. However, mutations have thus far been identified in highly enriched cohorts and the tumor spectrum among individuals with a broader phenotype undergoing multi-gene panel testing (MGPT) has not been described. Other genes associated with familial RCC have been established, such as FLCN (Birt-Hogg Dube syndrome) and VHL (von Hippel Lindau), but the proportion of BAP1 mutations in individuals with RCC is not yet known. Here we aim to describe the clinical features of individuals with BAP1 mutations identified from a clinical laboratory cohort, and to estimate the frequency of BAP1 mutations in individuals with kidney cancer.

Methods: Since May 2015, a total of 6956 tests have been ordered that include BAP1 at our diagnostic laboratory. Retrospective data review yielded molecular and clinical details for individuals with identified mutations.

Results: Thirteen individuals with BAP1 mutations have been identified. Cancer diagnoses in probands and family members consist of breast cancer (reported in 69.2% of kindreds), RCC (61.5%), melanoma (61.5%), mesothelioma (46.2%), lung cancer (46.2%), non-melanoma skin cancer (30.8%), and cholangiocarcinoma (15.4%). Among probands with kidney cancer undergoing MGPT (n=1012), there is no difference in mutation rate of BAP1 compared to VHL (n=3; OR 2.01 p=0.51) or FLCN (n=10; OR 0.598 p=0.45).

Conclusions: Cancer histories in our laboratory-selected cohort of BAP1 mutation carriers are consistent with those reported in the clinical literature, lending credence to the notion that BAP1 tumor predisposition syndrome is highly penetrant and consists of a constellation of several core cancers. The observation of breast, lung, non-melanoma skin cancer, and cholangiocarcinoma has also been reported in the literature and warrants further study. Our results suggest that BAP1 mutations are found at a similar frequency as other well-known kidney cancer genes, supporting its position as an important differential when considering genetic testing for RCC.