Frequent germline alterations in uveal melanoma patients referred for genetic counseling

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Purpose

About 10% of uveal melanomas (UM) patients have germline pathogenic variants in cancer genes with *BAP1* being the most common (1%). National Comprehensive Cancer Network (NCCN) guidelines recommend referral to genetics and genetic testing in patients with 1) Early age of diagnosis (≤30 years of age); 2) History of other primary cancers in the patient; 3) Family or personal history of other cancers known to be associated with a hereditary syndrome. The following study evaluated the outcomes of clinical testing for patients with UM referred to our clinical cancer genetics program.

Methods

UM patients meeting clinical criteria were referred for genetic counseling, offered the Ambry CancerNext Expanded 77-gene panel, and enrolled in an IRB-approved protocol. A retrospective chart review was conducted on the UM patients seen by a genetic counselor in The Ohio State University Cancer Genetics Clinic between 5/1/2021-8/1/2023. Reflex whole exome sequencing was performed for patients with no detectable variants in the 77 tested genes.

Results

A total of 56 individuals with UM were seen for genetic counseling. Of these patients, 19 were men (34.0%), and 37 (66.0%) were women. Forty-three (76.8%) individuals underwent clinical genetic testing. Seven (16.3%) individuals tested positive for pathogenic variants in cancer genes (*BAP1, BLM, BRCA1, BRCA2, MUTYH, POT1, XRCC2);* however, 2 were in genes *BLM* and *MUTYH* which are considered autosomal recessive. Twelve (21.4%) had a variant of uncertain significance (VUS) in cancer genes (*POT1, SMARCA4, CTNNA1, RECQL, CHEK2, CDH1, CDKN2A, AXIN2, MET, LZTR1, BRIP1, PMS2* and *MET),* while 27 (62.8%) tested negative. The BLM carrier also had a VUS in the *LZTR1* gene.

Of the 13 individuals that did not proceed with clinical genetic testing, most consented for research whole exome testing.

Conclusions

Genetic heterogeneity is observed in patients with hereditary predisposition to UM with alterations in multiple genes. The NCCN guidelines are useful in prioritization of UM patients for genetic testing. Currently only *BAP1* has definitive association with UM. Functional studies to assess the association of these other genes with UM are needed.