Genetics of uveal melanoma

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Mohamed H. Abdel-Rahman[*1,2], Maha Hussein[1], Peter Johansson[3], Lindsey Byrne[2], Reham Abdalla[1], Joseph McElroy[4], Isabella Gray[1], Fredrick H. Davidorf[1], Nicholas Hayward[3], Colleen M. Cebulla[1]*

[1]Ophthalmology and Visual Sciences, The Ohio State University Wexner Medical Center, Columbus, Ohio, United States; [2]Division of Human Genetics, The Ohio State University Wexner Medical Center, Columbus, Ohio, United States; [3]QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia; [4]Center for Biostatistics, The Ohio State University Wexner Medical Center, Columbus, Ohio, United States

Disclosures: Mohamed H. Abdel-Rahman: Code N (No Commercial Relationship) | Maha Hussein: Code N (No Commercial Relationship) | Peter Johansson: Code N (No Commercial Relationship) | Lindsey Byrne: Code N (No Commercial Relationship) | Reham Abdalla: Code N (No Commercial Relationship) | Joseph McElroy: Code N (No Commercial Relationship) | Isabella Gray: Code N (No Commercial Relationship) | Fredrick H. Davidorf: Code N (No Commercial Relationship) | Nicholas Hayward: Code N (No Commercial Relationship) | Colleen M. Cebulla: Code N (No Commercial Relationship)

Purpose

About 12% of uveal melanoma (UM) patients have features suggestive of hereditary cancer predisposition including young age of onset, bilateral tumors, strong personal/family history of cancers. Germline mutation in BAP1 gene explains only 1-2% of these patients, suggesting the existence of other candidate genes. The goal of this study was to better characterize moderate/high-penetrant genetic predisposition to UM.

Methods

A cohort of 464 UM patients UM enriched for those with a strong personal and/or family history of cancer, was studied. This included 52 with familial UM (FUM) and 43 with early-onset UM (diagnosed at ≤35 years). These patients were seen or referred to the Department of Ophthalmology, The Ohio State University and enrolled through IRB approved protocols. Patients initially underwent testing for pathogenic/likely pathogenic (P/LP) variants in *BAP1* through single-gene testing or using a 77-gene multigene panel. Those with no detectable P/LP in known cancer genes were further studied by whole exome sequencing (WES). We focused on rare P/LP variants (minor allele frequency <0.00001), in high/moderate penetrant cancer genes listed in the Catalogue of Somatic Mutations in Cancer (COSMIC).

Results

Genetic testing detected germline P/LP variants in established cancer genes in 82/464 patients (17.9%). The frequency of these variants was higher in FUM cases (20/52, 43.1%) compared to sporadic UM cases (62/412, 15.0%). The difference was statistically significant (p=0.0001). *BAP1* was the most frequently mutated gene, with P/LP variants observed in 16 patients, including 12/52 (23%) of FUM cases and 4/412 (~1%) of none-FUM cases. In sixteen other genes, P/LP variants were observed in at least two cases each. The most commonly affected pathways were DNA damage repair and telomere integrity. *MBD4* P/LP variants were identified in three patients, including one FUM case. Interestingly, the variant did not segregate with another UM case in that FUM family.

Conclusions

Germline pathogenic variants in BAP1 are the most common genetic alterations in UM patients, particularly in those with FUM. Germline P/LP variants in other genes, especially those involved in DNA damage repair and telomere integrity pathways, may also contribute to predisposition to this rare cancer. Obtaining a comprehensive cancer history and referring patients with a strong personal or family history of cancer is crucial for the proper management of patients and their at-risk family members.