Gene in eye melanomas linked to good prognosis

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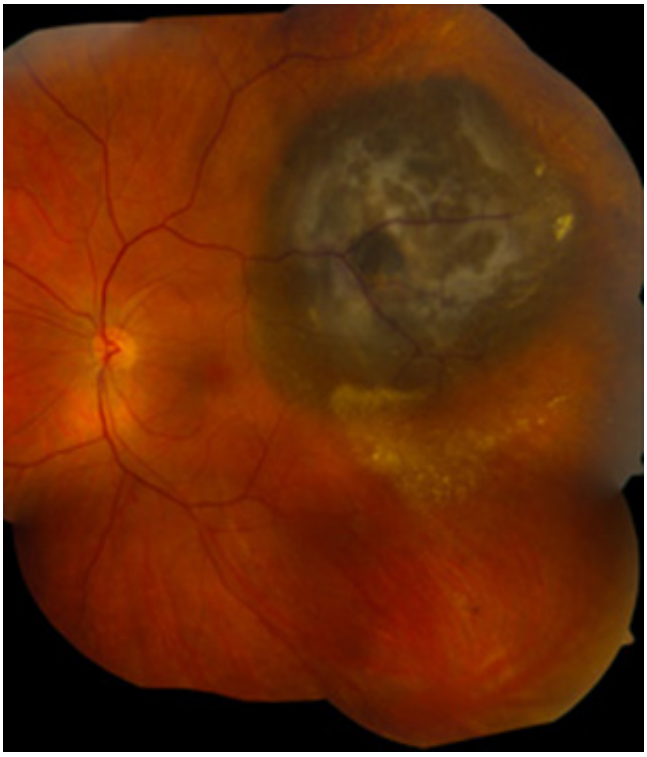

A melanoma that develop in the eye (above) often are fatal. But uveal melanoma tumors that have mutations in the SF3B1 gene are more likely to have a good outcome, suggests new research at Washington University School of Medicine in St. Louis. Credit: Harbour laboratory

Melanomas that develop in the eye often are fatal. Now, scientists at Washington University School of Medicine in St. Louis report they have identified a mutated gene in melanoma tumors of the eye that appears to

predict a good outcome.

The research is published in the advance online edition of Nature Genetics.

"We found mutations in a gene called SF3B1," says senior author Anne Bowcock, PhD, professor of genetics. "The good news is that these mutations develop in a distinct subtype of melanomas in the eye that are unlikely to spread and become deadly."

Eye tumors called uveal melanomas occur in about 2,000 patients a year, making up about 5 percent of all melanomas. In many patients, there are no symptoms, and the tumors become fatal when they spread to the liver.

Several years ago, Bowcock and the study's lead author, J. William Harbour, MD, a former Washington University eye surgeon who is now at the University of Miami, identified a commonly mutated gene, BAP1, in patients with uveal melanomas.

They found BAP1 alterations in about 80 percent of uveal melanomas with a poor prognosis, called class II tumors. About 75 percent of patients with these tumors die within five years, a sharp contrast to the generally favorable outcomes of patients whose tumors don't have BAP1 mutations, called class I.

For the new study, Bowcock and her colleagues initially sequenced the DNA of uveal melanomas from 18 patients whose BAP1 status was already known. Seven had no BAP1 mutations (class I tumors), and 11 had BAP1 mutations (class II tumors).

The researchers' analysis uncovered alterations in the SF3B1 gene in three of the patients.

"This is the first time mutations in this gene have been found in uveal melanoma," says Bowcock, who also is a professor of pediatrics and of medicine.

As part of the current study, the researchers also looked for SF3B1 mutations in uveal melanoma tumors from 102 patients, finding it in nearly 20 percent of them. Mutations in the gene were linked to favorable features, including a younger age at diagnosis and a far lower metastasis rate.

Interestingly, SF3B1 mutations always occurred at the same site of the gene. And the SF3B1 and BAP1 mutations were found to be almost mutually exclusive, meaning that if patients had a mutation in one of the genes, they were unlikely to have a mutation in the other.

"This suggests mutations in these genes may represent alternative pathways in tumor progression," Bowcock says.

The SF3B1 gene also has been reported recently by other researchers to be mutated in a pre-leukemia illness called myelodysplastic syndrome. For these patients, SF3B1 mutations mean the condition is less likely to develop into a full-blown leukemia. Changes in the SF3B1 gene also have been found in chronic lymphocytic leukemia and less frequently in breast cancer and other solid tumors. The gene's link to prognosis is unclear for these cancers.

Normally, the SF3B1 gene is involved in converting DNA's chemical cousin, RNA, into messenger RNA. This messenger molecule carries DNA's code and serves as a template for making proteins. The researchers don't yet understand how mutations in this gene are involved in cancer but it's the next step of their research.

"We want to understand the functional consequences of mutations in

SF3B1," Bowcock says. "How are changes in this gene linked to cancer development? This is the fourth gene known to be mutated in uveal melanoma along with BAP1 and the genes GNAQ and GNA11. A complete understanding of the molecular basis of this tumor will be invaluable in predicting prognosis and in the identification and development of novel treatments for this cancer."

More information: Harbour JW, Roberson EDO, Anbunathan H, Onken MD, Worley LA, Bowcock AM. Recurrent mutations at codon 625 of the splicing factor SF3B1 in uveal melanoma. *Nature Genetics*. Jan. 14, 2012.

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