SF3B1 mutations are associated with alternative splicing in uveal melanoma.
Cancer discovery : 1122-9 : DOI : 10.1158/2159-8290.CD-13-0330

Summary

Uveal melanoma, the most common eye malignancy, causes severe visual morbidity and is fatal in approximately 50% of patients. Primary uveal melanoma can be cured by surgery or radiotherapy, but the metastatic disease is treatment refractory. To understand comprehensively uveal melanoma genetics, we conducted single-nucleotide polymorphism arrays and whole-genome sequencing on 12 primary uveal melanomas. We observed only approximately 2,000 predicted somatic single-nucleotide variants per tumor and low levels of aneuploidy. We did not observe an ultraviolet radiation DNA damage signature, but identified SF3B1 mutations in three samples and a further 15 mutations in an extension cohort of 105 samples. SF3B1 mutations were associated with good prognosis and were rarely coincident with BAP1 mutations. SF3B1 encodes a component of the spliceosome, and RNA sequencing revealed that SF3B1 mutations were associated with differential alternative splicing of protein coding genes, including ABCC5 and UQCC, and of the long noncoding RNA CRNDE.
responsible for long-segment aberrations. Co-occurrence of two genomic features—LOH of 13q13 and 14q32—was found to predict BRCA2 status with 90% of sensitivity and 87% of specificity in discovery series of high-grade HER2-negative IDCs and 100% of sensitivity and 88% of specificity in an independent series of 58 IDCs. Estimated positive predictive value was 17.2% (confidence interval: 6.7-33.5) in the whole series. In conclusion, the simplified BRCA2 classifier based on the co-occurrence of LOH at 13q13 and 14q32 could provide an indication to test for BRCA2 mutation in patients with ER-positive IDC.

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Germline BAP1 mutations predispose to renal cell carcinomas.

Summary

The genetic cause of some familial nonsyndromic renal cell carcinomas (RCC) defined by at least two affected first-degree relatives is unknown. By combining whole-exome sequencing and tumor profiling in a family prone to cases of RCC, we identified a germline BAP1 mutation c.277A>G (p.Thr93Ala) as the probable genetic basis of RCC predisposition. This mutation segregated with all four RCC-affected relatives. Furthermore, BAP1 was found to be inactivated in RCC-affected individuals from this family. No BAP1 mutations were identified in 32 familial cases presenting with only RCC. We then screened for germline BAP1 deleterious mutations in familial aggregations of cancers within the spectrum of the recently described BAP1-associated tumor predisposition syndrome, including uveal melanoma, malignant pleural mesothelioma, and cutaneous melanoma. Among the 11 families that included individuals identified as carrying germline deleterious BAP1 mutations, 6 families presented with 9 RCC-affected individuals, demonstrating a significantly increased risk for RCC. This strongly argues that RCC belongs to the BAP1 syndrome and that BAP1 is a RCC-predisposition gene.


Designs and challenges for personalized medicine studies in oncology: focus on
the SHIVA trial.

Targeted oncology : 253-65 : DOI : 10.1007/s11523-012-0237-6

Summary

Personalized medicine is defined by the National Cancer Institute as “a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.” In oncology, the term “personalized medicine” arose with the emergence of molecularly targeted agents. The prescription of approved molecularly targeted agents to cancer patients currently relies on the primary tumor location and histological subtype. Predictive biomarkers of efficacy of these modern agents have been exclusively validated in specific tumor types. A major concern today is to determine whether the prescription of molecularly targeted therapies based on tumor molecular abnormalities, independently of primary tumor location and histology, would improve the outcome of cancer patients. This new paradigm requires prospective validation before being implemented in clinical practice. In this paper, we will first review different designs, including observational cohorts, as well as nonrandomized and randomized clinical trials, that have been recently proposed to evaluate the relevance of this approach, and further discuss their advantages and drawbacks. The design of the SHIVA trial, a randomized proof-of-concept phase II trial comparing therapy based on tumor molecular profiling versus conventional therapy in patients with refractory cancer will be detailed. Finally, we will discuss the multiple challenges associated with the implementation of personalized medicine in oncology, as well as perspectives for the future.