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A Melanoma Subtype: Uveal Melanoma

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To the Editor

Melanoma is a heterogeneous cancer consisting of different subsets. Uveal melanoma is a distinct subtype with clinical, biologic, and genetic differences from cutaneous melanoma.¹ It arises from melanocytes of the iris, ciliary body or the choroid, the latter being the most common location. Predisposing factors include uveal nevus and nevus of Ota. It is an aggressive tumor with approximately half of patients resulting in metastasis. The site of metastasis is the liver due to hematogenous spread. In contrast to cutaneous melanoma, lymphatic dissemination does not occur due to an absence of lymphatic drainage of the ocular interior. The cytogenetic abnormalities (chromosomal aberrations) of the tumor and gene expression profiles are different from cutaneous melanoma.¹ Monosomy 3 and gain of chromosome 8q within the tumor associate with a metastatic phenotype whereas gain of chromosome 6p occurs in tumors with low metastatic risk. Similarly, gene expression signatures accurately distinguish tumors at low metastatic and high metastatic risk.¹ Somatic genetic alterations observed in uveal melanoma show differences compared to cutaneous melanoma. Gain-of-function mutations in *BRAF* (40-50%) or *NRAS* (15-25%) are common among cutaneous melanomas of the trunk and extremities.² Increase gene dosage or mutations of *KIT* (39%) are observed among acral melanomas.³ *BRAF*, *NRAS*, *KIT* mutations are extremely rare in uveal melanoma.⁴ These genetic alterations lead to activation of the RAS-ERK pathway that is critical for proliferation, survival, migration, and differentiation signals and is virtually activated in the majority of melanomas.

Recently, gain-of-function mutations in the *GNAQ* gene that leads to RAS-ERK activation have been reported in uveal melanoma (83%) as well as in other melanocytic tumors (summarized in Table 1).⁵⁻⁸ The mutational profile of *GNAQ* has not been validated in large cohorts of cutaneous melanoma. Here, we report sequencing of the hotspot regions of the *GNAQ* gene (exon 5) as described previously⁵ in a cohort of cutaneous melanomas (n=122) consisting of melanomas of the trunk and extremities (n=83), acral sites (n=25), and unknown sites (n=14). Due to sequence homology to *GNAQ*, mutations in *GNAI1* gene were also tested. *BRAF* mutations were found in 53 (44%) and *NRAS* in 23 cases (19%), however no mutations in *GNAQ* or *GNAI1* were identified. This study validates recent findings that somatic mutations in *GNAQ* are rare, if any, among melanomas that arise from epidermal melanocytes of the trunk, extremities and acral sites.

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Benign melanocytic proliferations have also been associated with somatic mutations of the oncogenes associated with melanoma suggesting that these events occur early during development of melanocytic tumors. Large number of nevi is a risk factor for cutaneous melanoma; *BRAF* mutations are common in these nevi.² Giant congenital melanocytic nevus is a risk factor for cutaneous melanoma; *NRAS* mutations are common in this nevus subset.⁹ *GNAQ* mutations are found in blue nevus and nevus of Ota. Of interest, nevus of Ota is a known risk for uveal melanoma.¹

In conclusion, mutations in *GNAQ* are unique to uveal melanoma subtype and are rare, if any, in cutaneous melanoma. A full characterization of the melanocyte development pathways as well as identification of genetic events underlying benign and malignant melanocytic tumors, functional characterization of these genetic events and clinical correlative studies will eventually lead to comprehensive understanding of melanocytic tumors.

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Table 1Frequency of *GNAQ* Mutations in Benign and Malignant Neoplasms

Neoplasm type	GNAQ mutations	Citation
Uveal melanoma	46-49%	Onken et al, Van Raamsdonk et al
Mucosal melanoma	0%	Van Raamsdonk et al, Present study
Cutaneous melanoma (acral sites)	0%	Van Raamsdonk et al, Present study
Cutaneous melanoma (non-acral sites with chronic sun-induced damage)	0-4%	Van Raamsdonk et al, Present study
Blue nevus	46-83%	Lamba et al, Van Raamsdonk et al
Malignant blue nevus	50%	Van Raamsdonk et al
Nevus of Ota	6-46%	Lamba et al, Van Raamsdonk et al
Congenital nevus	0%	Van Raamsdonk et al
Deep penetrating nevus	0%	Van Raamsdonk et al
Spitz nevus	0%	Van Raamsdonk et al
Primary melanocytic neoplasms of the central nervous system	37%	Kusters-Vandeveldt et al
Other neoplasms (carcinoma of the breast, colon, bladder, lung, ovarian, pancreas, thyroid; gastrointestinal stromal tumor; glioma; acute myelogenous leukemia)	0%	Lamba et al

ND, not determined