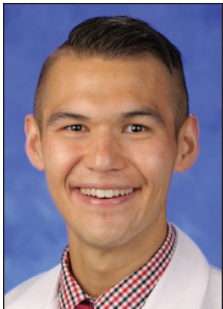


Genetic mutations

by Matthew Helm, MD and Paul Wirth, MD

Melanocytic Lesions		
Gene	Lesion	Function
C-kit	Mucosal and acral melanoma, melanoma on chronic sun-damaged skin	Encodes CD117, a transmembrane receptor tyrosine kinase protein
BRAF (V600E most commonly)	Melanoma on non-chronic sun-damaged skin, Common nevi	Encodes the serine/threonine-protein kinase B-Raf
NRAS	Nodular melanoma, non-CSD melanoma, congenital melanocytic nevi (CMN), common nevi	Member of the RAS gene family
Loss of BAP1	Atypical spitzoid tumors with epitheloid Spitz nevi (BAPoma), melanoma, uveal melanoma, renal cell carcinoma	Loss of deubiquitination by BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase).
TERT-p	Advanced melanoma	Telomerase reverse transcriptase (TERT) promoter mutations are associated with poor prognosis.
Activating mutation GNAQ	Uveal melanoma, Nevus of Ota, blue nevus	Transmembrane domain receptors catalyzes intracellular signaling pathways and exchange of GDP for GTP.
GNA11	Uveal melanoma, blue nevus, malignant blue nevus	Works with the paralogue GNAQ.
HRAS mutations/11p gains	Spitz nevus-more common after puberty	Activating HRAS mutation in agminated spitz nevi and mosaicism
P16 loss	Atypical spitz tumors and spitzoid melanoma. Often misdiagnosed as infantile hemangioma due to erythematous color and prominent telangiectasia.	Loss of this INK4 cyclin-dependent kinase inhibitors (CDKIs) prevents withdrawal from cell cycle progression. P16 staining argues against 9p21 loss.



Matthew Helm, MD, is a PGY-4 dermatology resident at Penn State Health, Milton S. Hershey Medical Center.



Paul Wirth, MD, is a PGY-3 dermatology resident at Penn State Health, Milton S. Hershey Medical Center.

Genetic mutations

by Matthew Helm, MD and Paul Wirth, MD

Melanocytic Lesions		
Gene	Lesion	Function
Homozygous loss of 9p21	Increase risk of metastasis and death in spitzoid tumor	Three tumor suppressor genes are found at this location: genes CDKN2A, CDKN2B, and MTAP.
CDKN2A	Familial atypical multiple mole melanoma syndrome (FAMMM), dysplastic nevi, melanoma, pancreatic cancer	Protein products p14 and p16 modulates cell cycle progression via p53 and Rb pathways.
CCND1/CDK4	CSD sites, acral and mucosal melanoma	Amplification leads to leads to increased phosphorylation of Rb gene allowing E2F to promote expression of genes that leads to the progression from G1 to the S phase.
Types of nevi, genomic associations, and phenotype		
Common and congenital melanocytic nevi	BRAF and NRAS	Maturation of nests
Blue nevi and related neoplasms	GNAQ and GNA11	Heavily pigmented dendritic melanocytes
Desmoplastic spitz	HRAS	Prominent fibrotic stroma
Spitz	ALK fusion	Plexiform growth pattern with large nests of fusiform to polygonal melanocytes in elongated nests.
Spitz	ROS-1 fusion	Well-circumscribed and dome-shaped
Spitz	NTRK1 fusion	Classical histology

Abbreviations

CSD – chronic sun damaged
CMN – congenital melanocytic nevi

References:

- Bastian BC. The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. *Annu Rev Pathol* 2014;9:239-71.
- Bennett DC. Genetics of melanoma progression: the rise and fall of cell senescence. *Pigment Cell Melanoma Res* 2016;29:122-40.
- Bolognia, Jean L., Joseph L. Jorizzo, and Julie V. Schaffer. *Dermatology*. Philadelphia: Elsevier Saunders, 2012.
- Dimonitsas E, Liakea A, Sakellariou S, Thymara I, Giannopoulos A, Stratigos A, Soura E, Saetta A, Korkolopoulou P. An update on molecular alterations in melanocytic tumors with emphasis on Spitzoid lesions. *Ann Transl Med* 2018;6(12):249. doi: 10.21037/atm.2018.05.23
- Wiesner T, Kutzner H, Cerroni L, et al. Genomic aberrations in spitzoid melanocytic tumours and their implications for diagnosis, prognosis and therapy. *Pathology* 2016;48:113-31.

Boards Fodders online!



In addition to this issue's Boards Fodder, you can download the new online Boards Fodder at www.aad.org/Directions. Go online for a new Boards Fodder web exclusive, **Testable fibrous and fibrohistiocytic proliferations of the skin: Facts and buzzwords** by Mohammed Shanshal, MD. The AAD now has more than 100 Boards Fodder study charts!

Check out the archives at www.aad.org/boardsfodder.

Got Boards?



Directions in Residency is currently accepting submissions for new Boards Fodder charts for 2020. Get published, impress your friends, and help out your fellow residents. Contact Dean Monti, dmonti@aad.org with your chart ideas.