Title

CDKN2A exon 1B deletion predisposing to melanoma and neural system tumour syndrome.

Journal

Clinical and Experimental Dermatology, 47(12)

Authors

Wong, Samantha

Martiniuc, Daniela

Kiuru, Maija

Publication Date

2022-12-01

DOI

10.1111/ced.15354

Peer reviewed

HHS Public Access

Author manuscript

Clin Exp Dermatol. Author manuscript; available in PMC 2023 December 01.

Published in final edited form as:

Clin Exp Dermatol. 2022 December ; 47(12): 2284–2285. doi:10.1111/ced.15354.

CDKN2A exon 1B deletion predisposing to melanoma and neural system tumor syndrome: a case report

Samantha L. Wong[1], **Daniela Martiniuc**[2], **Maija Kiuru**[1,3]

[1]Department of Dermatology, University of California, Davis, Sacramento, CA, USA

[2]Hereditary Cancer Program, Comprehensive Cancer Center, University of California, Davis, Sacramento, CA, USA

[3]Department of Pathology and Laboratory Medicine, University of California, Davis, Sacramento, CA, USA

CDKN2A, the most mutated gene causing hereditary melanoma, encodes two major proteins, p16 and p14(ARF), through alternative splicing involving exon 1A and 1B, respectively.[1] While early-onset melanoma is associated with variants affecting both transcripts, large deletions or mutations, including splice site mutations, affecting the p14(ARF) protein are exceedingly rare and are associated with a distinct clinical phenotype of melanoma and neural system tumor syndrome (melanoma-astrocytoma syndrome).[1,2] In addition to astrocytoma, nerve sheath tumors (neurilemmoma, neurofibroma) and glioma have been reported.[3,4] p14ARF is thought to regulate the cell cycle by blocking HDM2-mediated degradation of p53 and apoptosis.[2] Herein, we describe a kindred with a *CDKN2A* deletion of exon 1B and multiple cutaneous melanomas, pancreatic cancer, neural tumors, and various malignancies.

A 55-year-old female presented for cancer genetics evaluation due to a history of multiple primary cutaneous melanomas and family history of melanoma, neurofibromas, and premenopausal breast, pancreatic, colon, and brain cancers. She had a history of melanoma dating over 40 years and received a clinical diagnosis of dysplastic nevus syndrome in childhood. Multiple melanomas had been removed over her extremities and trunk, and metastatic melanoma to the left inguinal nodes was initially identified 13 years prior, with disease progression several years later.

The patient's family history was significant for cutaneous melanomas in multiple relatives, including her father, paternal grandfather, three sisters and a nephew from ages 15 to 58. Additional tumor diagnoses in these and other relatives included neurofibromas, pineal parenchymal tumor, and breast, colon, and pancreatic cancers (Figure 1).

A targeted gene panel was performed: *ATM, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A* (p14ARF)*, CDKN2A* (p16INK4a)*, CHEK2, MC1R, NBN,*

Corresponding author: Maija Kiuru MD, PhD., mkiuru@ucdavis.edu.

Conflicts of interest: None declared.

Ethics statement: Informed consent was obtained.

NF1, PALB2, POT1, PTEN, RAD50, RB1, STK11, TERT, TP53, *MITF (c.952G>A, p.Glu318Lys variant only).* Germline analysis in our patient detected a heterozygous pathogenic *CDKN2A* mutation, specifically deletion of exon 1B. The testing laboratory did not determine the breakpoints of the deletion, but it is not expected to disrupt the coding sequence of the p16 transcript. Between the time of our patient's initial genetics evaluation and completion of testing, we were notified that her relatives with neurofibromas and melanoma carried the same *CDKN2A* mutation. Our patient died of complications from metastatic melanoma soon after her molecular diagnosis. Recommendations for cancer screening, genetic counseling, and testing were provided for at-risk relatives.

Per National Comprehensive Cancer Network guidelines, clinical genetic testing for *CDKN2A*, which includes exon 1B testing, is recommended in the presence of three or more invasive primary cutaneous melanomas, or a mix of melanoma, pancreatic cancer, and/or astrocytoma in an individual or a family. We propose that indications for considering *CDKN2A* as a differential diagnosis may need to include nervous system tumors beyond astrocytomas to ensure a timely and accurate diagnosis. Indeed, some of these individuals have been clinically misdiagnosed with neurofibromatosis type 1 in part due to the presence of multiple neurofibromas.[1] The kindred in our study included a case of fatal pineal parenchymal tumor; further work is needed to explore possible association between germline *CDKN2A* mutations affecting the p14(ARF) and the risk of pineal parenchymal tumors. Notably, 14% of pineoblastomas show loss of *CDKN2A*.[5]

In conclusion, it is imperative to recognize the increased risk of neural tumors in a subset of patients with hereditary melanoma. Clinicians managing individuals with *CDKN2A* mutations affecting p14(ARF) should be aware of the likely increased risk of neural tumors outside of astrocytoma, and to consider the patient's family history for tailored surveillance recommendations as current medical management guidelines are directed toward surveillance for melanoma and pancreatic cancer. At-risk family members should seek genetic counseling services for familial genetic testing and should receive regular melanoma screening.

Funding:

National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, through grant #K23AR074530 (MK)

References

1. Soura E, Eliades PJ, Shannon K, Stratigos AJ, Tsao H. Hereditary melanoma: Update on syndromes and management: Genetics of familial atypical multiple mole melanoma syndrome. J Am Acad Dermatol 2016; 74: 395–407; quiz 8–10. [PubMed: 26892650]
2. Goldstein AM, Chan M, Harland M et al. High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. Cancer Res 2006; 66: 9818–28. [PubMed: 17047042]
3. Randerson-Moor JA, Harland M, Williams S et al. A germline deletion of p14(ARF) but not CDKN2A in a melanoma-neural system tumour syndrome family. Hum Mol Genet 2001; 10: 55–62. [PubMed: 11136714]
4. Tachibana I, Smith JS, Sato K et al. Investigation of germline PTEN, p53, p16(INK4A)/p14(ARF), and CDK4 alterations in familial glioma. Am J Med Genet 2000; 92: 136–41. [PubMed: 10797439]

5. Miller S, Rogers HA, Lyon P et al. Genome-wide molecular characterization of central nervous system primitive neuroectodermal tumor and pineoblastoma. Neuro Oncol 2011; 13: 866–79. [PubMed: 21798848]

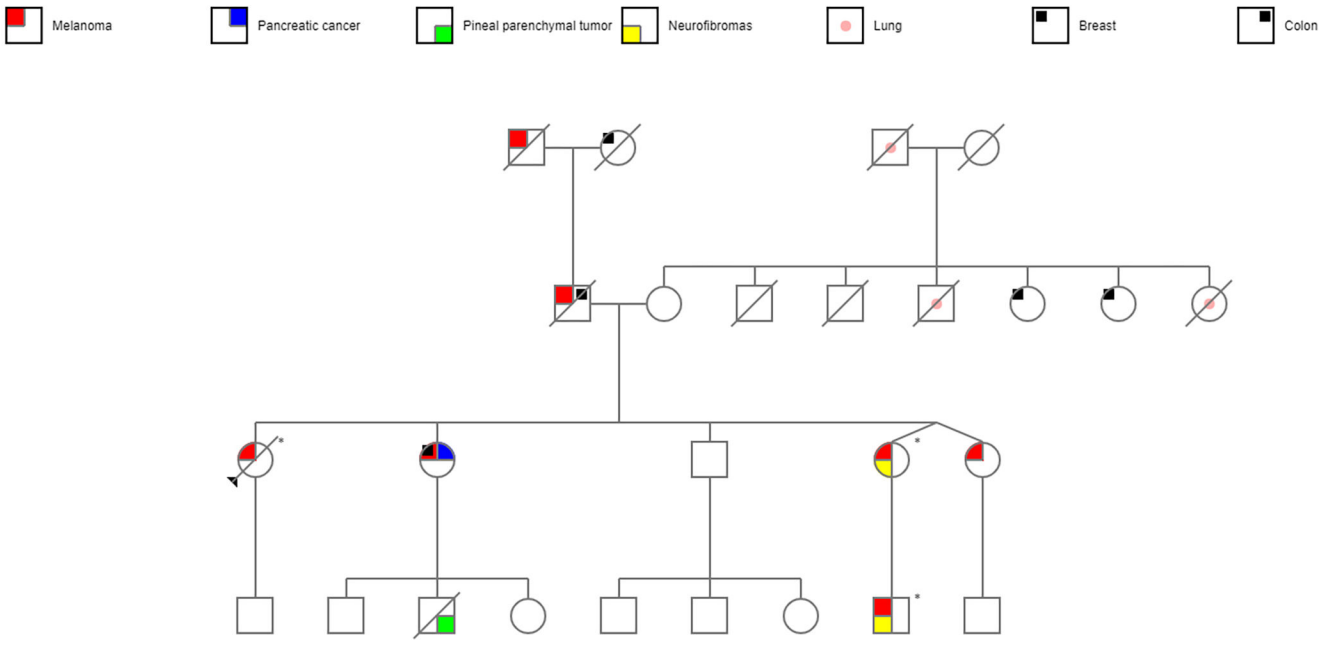

Figure 1.
Pedigree of the family. Asterisk indicates carrier of CDKN2A exon 1B deletion.