BUB1B mutation in a woman with cutaneous melanoma and multiple other primary malignancies

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Introduction

•Cutaneous melanoma results from the malignant transformation of melanocytes in skin and accounts for 75% of deaths related to skin cancer[1].

•Between 5 to 12% of melanoma cases can be attributed to hereditary melanoma, melanoma caused by inherited germline mutations in melanoma predisposition genes[2]

•Although several inherited melanoma predisposition syndromes have been identified, a subset of melanoma families lack pathogenic mutations in known highly penetrant predisposition genes, including *CDKN2A, CDK4,* and *BAP1* [3]

•Here we report the case of a woman with a history of melanoma and multiple primary tumors with one pathogenic germline mutation in *BUB1B*

Aim

- The aim of the study was to identify a germline mutation causing an increased susceptibility to melanoma and other malignancies in a 74-year-old woman with two distinct cutaneous melanomas, and multiple other primary malignancies

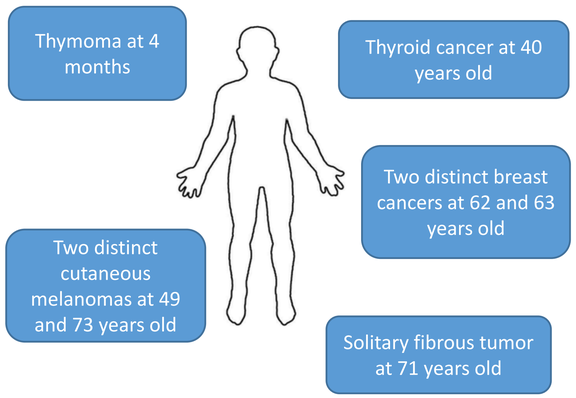
Materials and Methods

- Approval for the study was obtained through the Institutional Review Board at University of California Davis.
- A personal and family history of malignancies was obtained
- Peripheral blood was collected, and DNA was extracted
- Comprehensive clinical genetic testing of 75 genes was performed
- Additional whole exome sequencing of normal and tumor DNA from patient's melanoma was performed
- Immunohistochemistry of *BUB1B* was performed using normal skin, nevus, and melanoma patient samples with corresponding controls

Results

- Patient had extensive history of primary malignancies at varying ages (Figure 1)
- Of note, these tumors included thymoma at the age of four months treated with radiation
- Additionally, patient had a history of multiple melanomas
- Family history included a brother with breast cancer at 68y, another brother with prostate cancer at 70y and cutaneous melanoma at unknown age, maternal grandmothers' sisters and their daughters with breast cancer at ages 49y, 51y, and their early 40s, respectively, maternal uncle with rectal cancer at 55y, and her father with an unknown urinary tract cancer at 96y
- Sequencing revealed one heterozygous pathogenic mutation c.2316C>G (p.Tyr772*) in the *BUB1B* gene (Figure 2)
- No additional pathogenic variants or variants of uncertain significance were detected in any of the other genes tested
- Immunohistochemistry showed no significant differences in *BUB1B* expression between patient's nevus and melanoma samples and corresponding sporadic nevus and tumor samples (Figure 3)

Figure 1: Schematic representation of patient's tumor history

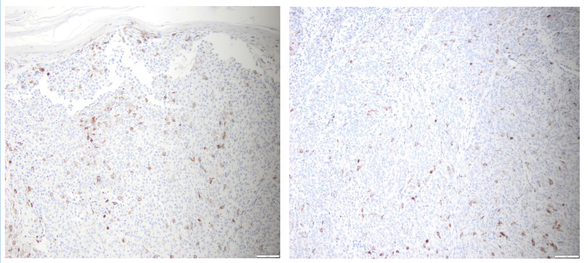


Results

Figure 2:The heterozygous stopgain *BUB1B* mutation (BUB1B:NM_001211:exon18:c.C2316G:p.Y772X) identified in the patient through whole-exome sequencing (Integrative Genomics Viewer v2.11.1; GRCh38)

Figure 3: A. Immunohistochemistry staining of *BUB1B* antibody performed on melanoma control at 10X magnification.
B. Immunohistochemsitry staining of *BUB1B* on melanoma of patient at 10X magnification.

A. B.



Conclusions

- *BUB1B* encodes a kinase involved in spindle checkpoint function, a process dysregulated in many cancer types[4-8]
- To date, germline pathogenic variants in *BUB1B* have rarely been implicated in inherited tumor predisposition[1,4]
- We propose that heterozygous pathogenic *BUB1B* variants may increase susceptibility to multiple primary tumors, including melanoma, and may explain this patient's history of multiple cancers
- Monoallelic and biallelic mutations in *BUB1B* have been associated with the development of mosaic variegated aneuploidy syndrome, a rare genetic disorder associated with high risk of childhood cancer[1,3,9,10]

Conclusions

- Biallelic *BUB1B* mutations have been implicated in predisposition to common adulthood cancers, including adenocarcinoma of colon and stomach[4].
- Furthermore, similar to our patient, one patient with melanoma, breast cancer and mesothelioma and germline heterozygous truncating *BUB1B* mutation was discovered in a study involving patients with melanoma and multiple other cancers[1]
- This case expands our knowledge of novel hereditary cancer genes that may increase risk for various malignancies
- Identification of novel genes associated with hereditary cancer risk is integral for optimal genetic counseling and appropriate cancer screening in at-risk individuals

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Acknowledgements

We are grateful to the patient for participating in this study. We also thank Iryna Rybak and Lan Yu for assistance with this study.