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Incidental MITF, p.E318K Pathogenic Variant in Three Independent Cases Undergoing Hereditary Cancer Risk Assessment

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Background

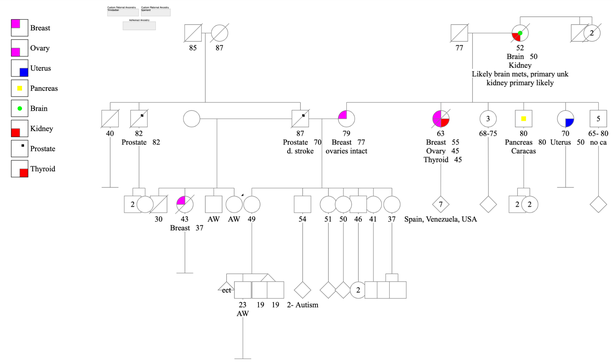
- The *MITF*, p.E318K mutation has been described as a rare risk factor for melanoma and renal cell carcinoma [2].
- Associated risks for the *MITF*, p.E318K mutation have been mostly ascertained by studying melanoma cohorts [1-3].
- Little is known about the incidence of *MITF*, p.E318K or the natural history of *MITF*, p.E318K carriers in non-melanoma cohorts.
- We describe three cases where the *MITF*, p.E318K mutation was incidentally identified during hereditary cancer risk assessment.

Clinical History

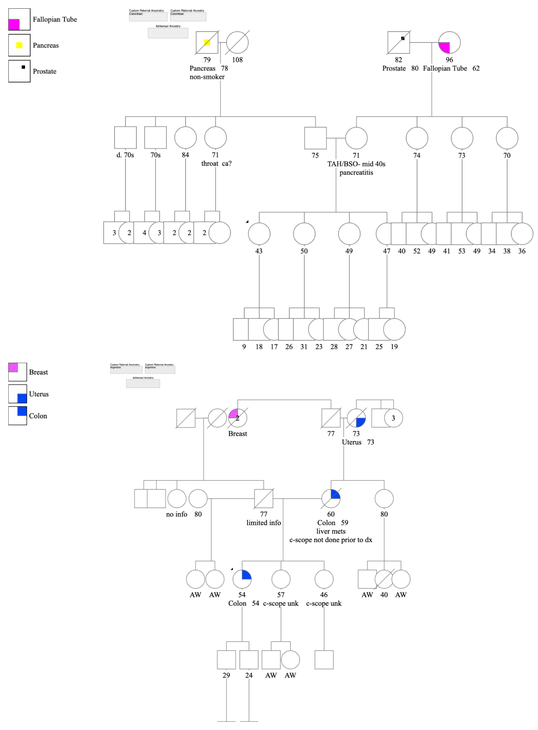
Clinical History		Cases		
		Case 1	Case 2	Case 3
Age		49	43	52
Gender (M/F)		Female	Female	Female
Ethnicity/ Race		Hispanic White	Hispanic White	Hispanic White
Personal history of cancer				Yes
Location and pathology	Treatment	None	None	• CRC • Adenocarcinoma at descending colon • Normal immunohistochemistry for Mismatch Repair (MMR) genes • Metastatic to the liver at diagnosis Palliative chemotherapy with FOLFOX and Avastin
Reason for referral		Family history of breast, ovarian and pancreatic cancer	Family history of fallopian tube cancer and pancreatic cancer	Newly diagnosed colon cancer. Family history of colon, endometrial, and breast cancer.
Met HBOC genetic testing NCCN guidelines at assessment?		**Yes**	**Yes**	No
Met Lynch Syndrome genetic testing NCCN guidelines at assessment?		No	No	**Yes**
Genetic testing pursued		*81-gene panel*	75-gene panel	67-gene panel
Assay		CustomNext-Cancer ®	CustomNext-Cancer ®	CancerNext-Expanded®

Family History

Case 1



Case 2



Case 3

Genetic Test Results

Genetic Test Results	Cases		
	Case 1	Case 2	Case 3
Pathogenic variants	***MITF*, c.952G>A; p.E318K** ***FLCN*, c.1579C>T**	***MITF*, c.952G>A; p.E318K**	***MITF*, c.952G>A; p.E318K**
Variants of Unknown Significance	*ATM*, c.6820G>A		*RAD51C*, c.719T>C *BRCA2*, c.9925GA

MITF Risks & Proposed Recommendations *

	Lifetime Risks	Screening	Age to begin
Melanoma	~5-20% (vs. ~2.5% USA population risk)	Annual full body dermatologic exam	~20 y *(Median age of onset 31-71 y [3])*
Renal Cell Carcinoma (RCC)	~8% (vs. 1.6% USA population risk)	Baseline urology evaluation Consideration of annual renal imaging with renal ultrasound. Consider alternating with MRI. Consideration of annual urinalysis	~25-30 y *(Median age of onset 35-72 y [4])*

** Based on available literature, geographic location, and screening guidelines for other genetic syndromes associated with melanoma and RCC*

Discussion

- As multigene panel testing continues to gain popularity in clinical practice, incidental pathogenic variants are also more commonly identified.
- The challenge of incidental findings is heightened in genes with limited data on lifetime risks and incomplete penetrance.
- We highlight the importance of the development of clinical guidelines for newly described hereditary cancer genes to standardize recommendations, better understand risks for carriers in other populations, and justify medical necessity for management changes based on incidental genetic test results.
- **Limitations:**
- Small sample size. Limited data on longitudinal follow-up to assess the clinical impact of incidental findings.

References

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