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Clinical Implications of Pathogenic Germline Variants in Small Intestine Neuroendocrine Tumors

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BACKGROUND: Hereditary susceptibility for NET tumors (NET) has been well-described in patients with rare, inherited genetic syndromes, including MEN1, von Hippel Lindau or tuberous sclerosis complex syndromes. An inherited basis for presumed "sporadic" NET has been suggested by evidence of familial clustering of NET tumors, and a documented higher incidence of second malignancies in patients and families with NET tumors.

METHODS: We performed germline analysis with an 83-gene, next generation sequencing panel using DNA from 90 individuals with SI-NET. Participants were identified from the clinically annotated Dana-Farber Cancer Institute Neuroendocrine and Carcinoid Tumors Program's prospectively collected database which includes over 1800 patients. The patients were selected based on patient-reported family and past medical history. The high risk features were categorized as diagnosis of SI-NET under the age of 40, personal history of a second cancer, and those with family history meeting National Comprehensive Cancer Network Guideline criteria for genetic testing. In those with identified pathogenic germline mutations, analysis of the tumor DNA for loss of heterozygosity will be performed utilizing the DFCI custom targeted next-generation sequencing platform.

RESULTS: Of the 90 patients evaluated, a pathogenic germline variant was identified in 8 patients: 4 had a personal history of a second cancer; 5 had a family history and met clinical criteria to undergo genetic testing. One patient

had a family history and a personal history of a second cancer. Pathogenic variants were identified in the following genes: CHEK2, RAD51C, BLM, RET, ATM, FH, and TP53. Somatic testing results are pending at the time of submission.

CONCLUSION: We demonstrate a 9% incidence of pathogenic germline variants in moderate to low penetrance genes associated with inherited susceptibility for malignancy not previously described in association with SI-NET.

Table 1.

Patient #	High Risk Criteria	Germline Variant locus
1	Personal history of SI-NET and family history (FH)	CHEK2 c.110delC (p.Thr367Metfs*15)
2	Personal history of SI-NET and FH	RAD51C c.181_182delCT(p.Leu61Alafs*11)
3	Personal history of SI-NET and FH	BLM c.3569delinsAA (p.Met1190Lysfs*27
4	Personal history of SI-NET, 2nd cancer and FH	RET c.2410G>A(p.Val804Met)
5	Personal history of SI-NET, 2nd cancer and FH	ATM c.7638_7646del (p.Arg2547_Ser2549del)
6	Personal history of SI-NET and FH	TP53 c.614A>G (p.Tyr205Cys)
7	Personal history of SI-NET and FH	FH c.1431_1433dupAAA (p.Lys477dup)
8	Personal history of SI-NET, 2nd cancer and FH	BLM c.2207_2212delinsTAGATTC (p.Tyr736Leufs*5)