Inherited Susceptibility to Biliary Tract and Ampullary Cancers

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BACKGROUND

- In recent years, significant advances have been made regarding hereditary predisposition to pancreatic cancer outside of classically described cancer syndromes such as hereditary breast and ovarian cancer (HBOC). Notably, results from exome and whole genome sequencing studies of pancreatic cancer families have identified *PALB2* and *ATM* as pancreatic cancer susceptibility genes, respectively.[1,2]
- Biliary tract and ampullary cancers can exhibit phenotypic overlap with pancreatic cancers and have also been recognized as components of hereditary cancer syndromes such as HBOC, Lynch syndrome and familial adenomatous polyposis.[3-5] However, these cancers are less common than pancreatic cancer and data is limited in comparison.
- We aim to explore the germline mutation spectrum in patients with biliary tract and ampullary cancers who underwent multigene panel testing for inherited cancer susceptibility.

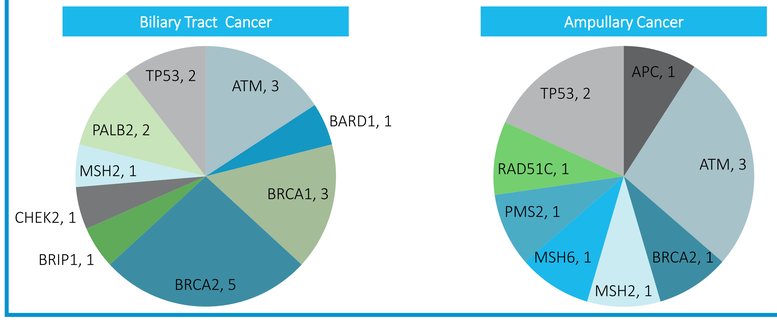
METHODS

- Clinical histories and molecular results were reviewed for individuals with a history of biliary tract (n=131, including gallbladder and bile duct cancers) or ampullary cancers (n=53), ascertained from a cohort of >140,000 patients who underwent hereditary cancer multigene panel testing of 5 to 49 genes at single laboratory between 03/2012 – 06/2016 (**Table 1**).
- Clinical history information was obtained from test requisition forms completed by ordering clinicians and from pedigrees/clinic notes, if provided.

Table 1. Demographics & Clinical History

	Characteristic	Biliary tract cancer		Ampullary cancer	
		n, positive (tested)	%	n, positive (tested)	%
Ethnicity	Asian	7 (131)	5.3	5 (53)	9.4
	Ashkenazi Jewish	9 (131)	6.9	3 (53)	5.7
	Caucasian	85 (131)	64.9	32 (53)	60.4
	Hispanic	7 (131)	5.3	3 (53)	5.7
	African American/Black	6 (131)	4.6%	0 (53)	0.0
	Other/Unknown	15 (131)	6.1	10 (53)	9.4
Gender	Male	41 (131)	31.3	23 (53)	43.4
	Female	90 (131)	68.7	30 (53)	56.6
Personal history	Biliary/ampullary cancer as first, synchronous, or only cancer	86 (127)	67.7	35 (52)	67.3
	Personal history of additional cancer(s)	64 (131)	48.9	24 (53)	45.3
	Median (IQR) age at diagnosis, years	58.0 (47.0, 65.5)		51.5 (46.3, 62.0)	

Figure 1. Pathogenic/Likely Pathogenic Variants Detected



RESULTS

- Pathogenic/likely pathogenic variants (PVs) were detected in 14.5% (19/131) of patients with biliary tract cancer and 20.8% (11/53) patients with ampullary cancer who underwent multigene panel testing (**Fig. 1**). This may be an underestimate since patients were tested for a varying number of genes depending on the panel ordered and some patients also screened negative on previous genetic testing.
- *BRCA2*, *BRCA1*, *ATM*, and *PALB2* were the most frequently mutated genes in patients with biliary tract cancers (**Table 2**). Similarly, *BRCA2* (3.9%), *ATM* (3.6%), and *PALB2* (1.5%) were among the most frequently mutated genes in 1819 pancreatic cancer patients from the same multigene panel cohort, demonstrating overlap in the germline mutation spectrum for pancreatic and biliary tract cancers.
- The number of ampullary cancer patients was more limited in comparison. Despite the small numbers, *ATM* was frequently mutated in ampullary cancer patients, with three PVs observed among 44 patients tested (6.8%).

REFERENCES

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Table 2. Mutation Frequency by Gene and Cancer Type

Cancer Type	Gene	n, positive (tested)	% positive	Other cancers and/or polyps reported in probands
Biliary tract	*ATM*	3 (106)	2.8	[1] melanoma (40s); [2] none; [3] none
	BARD1	1 (97)	1.0	none
	BRCA1	3 (108)	2.8	[1] prostate (50s); [2] bladder (70s), melanoma (70s); [3] none
	BRCA2	5 (108)	4.6	[1] lymphoma (20s); [2] bilateral breast (40s); [3] CRC (50s), ureter (60s), bladder (60s); [4] breast (30s); [5] none
	BRIP1	1 (97)	1.0	ovarian (60s)
	CHEK2	1 (111)	0.9	none
	MSH2	1 (123)	0.8	none
	PALB2	2 (110)	1.8	[1] prostate (30s); [2] bilateral breast (40s, 60s)
	TP53	2 (130)	1.5	[1] breast (40s); [2] prostate (72), pancreatic (72)
Ampullary	*APC*	1 (52)	1.9	CRC (30s), testicular (60s)
	ATM	3 (44)	6.8	[1] breast (70s), CRC (70s); [2] none; [3] none
	BRCA2	1 (42)	2.4	none
	MSH2	1 (53)	1.9	CRC (40s), 10-19 adenomatous polyps
	MSH6	1 (53)	1.9	2-5 adenomatous polyps
	PMS2	1 (53)	1.9	2-5 adenomatous polyps
	RAD51C	1 (32)	3.1	non-Hodgkins lymphoma (40s), anal (60s)
	TP53	2 (53)	3.8	[1] ovarian (30s) and desmoid tumor (50s); [2] none

CONCLUSIONS

- While limited in size, results from this exploratory study suggest that the spectrum of germline mutations among biliary tract and ampullary cancer patients spans a range of cancer predisposition genes, many of which overlap with pancreatic cancer susceptibility.
- Almost all mutations detected in these patients are considered clinically actionable with respect to other cancer types, thereby presenting an opportunity for patients and families to be appropriately managed.
- The mutation detection rate observed in this cohort demonstrates the need for controlled studies aimed at assessing mutation frequencies and cancer risks among lesser selected (and larger) ampullary and biliary tract cancer cohorts.

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