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PRESENTER: Holly LaDuca
PRESENTER (EMAIL ONLY): hladuca@ambrygen.com

Abstract

TITLE: Inherited susceptibility to biliary tract and ampullary cancers

AUTHORS (LAST NAME, FIRST NAME): LaDuca, Holly[1]; Black, Mary Helen[1]; Speare, Virginia[1]; Couch, Fergus J.[2]

INSTITUTIONS (ALL):

1. Clinical Diagnostics, Ambry Genetics, Downers Grove, IL, United States.
2. Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, United States.

ABSTRACT BODY:

Abstract Body: 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. Notably, results from exome and whole genome sequencing studies of pancreatic cancer families have identified *PALB2* and *ATM* as pancreatic cancer susceptibility genes. 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 Lynch syndrome and familial adenomatous polyposis. 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 (MGPT) 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 MGPT at single commercial laboratory. Clinical history information was obtained from test requisition forms completed by ordering clinicians and from pedigrees/clinic notes, if provided.

RESULTS: The majority of patients in this cohort were Caucasian (63.6%) and female (65.2%) and nearly half (47.8%) reported a history of at least one additional cancer primary. The median (IQR) age at diagnosis was 58.0 (47.0, 65.5) years for biliary tract and 51.5 (46.3, 62.0) years for ampullary cancers. Pathogenic/likely pathogenic variants were detected in 20.8% of ampullary cancer patients and 14.5% of biliary tract cancer patients (Table). *BRCA2* (4.6%), *BRCA1* (2.8%), and *ATM* (2.8%) were the most frequently mutated genes among patients with biliary tract cancers and *ATM* (6.8%) and *TP53* (3.8%) were most frequently mutated among patients with ampullary cancers. 50% of *APC*, *BRCA1/2*, *MSH2*, *MSH6*, *PMS2* and *TP53* mutation carriers did not meet testing criteria for the respective syndrome (n=9/18) based on the clinical history provided.

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 this study 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 ampullary and biliary tract cancer cohorts.

TABLE:

.	Biliary Tract (N=131)			Ampullary (N=53)		
Gene	N, positive	N, tested*	% positive	N, positive	N, tested*	% positive
APC	0	103	0.0%	1	52	1.9%
ATM	3	106	2.8%	3	44	6.8%

BARD1	1	97	1.0%	0	32	0.0%
BRCA1	3	108	2.8%	0	42	0.0%
BRCA2	5	108	4.6%	1	42	2.4%
BRIP1	1	97	1.0%	0	32	0.0%
CHEK2	1	111	0.9%	0	41	0.0%
MSH2	1	123	0.8%	1	53	1.9%
MSH6	0	123	0.0%	1	53	1.9%
PALB2	2	110	1.8%	0	44	0.0%
PMS2	0	123	0.0%	1	53	1.9%
RAD51C	0	97	0.0%	1	32	3.1%
TP53	2	130	1.5%	2	53	3.8%

*The total number tested varies by gene, as not all patients were tested with the same multigene panel.

(No Image Selected)

DISCLOSURE

The following authors have completed their 2017 DDW disclosure:: Holly LaDuca: Disclosure completed | Mary Helen Black: Disclosure completed | Virginia Speare: Disclosure completed | Fergus Couch: No Answer.