GC-107

Double germline variants in different cancer predisposition genes: a laboratory summary of findings

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I. Background

The increasing use of hereditary cancer multi-gene panels has identified more individuals with pathogenic (PVs) or likely pathogenic variants (LPVs) in two or more genes.[1] These patients are at increased risk for multiple primary cancers which may pose new management and treatment challenges. Currently, data on genotype-phenotype correlations and corresponding management guidelines are limited. LabCorp offers 12 hereditary cancer multi-gene panels, in addition to separate *BRCA* and Lynch syndrome panels. The aim of this study is to describe a cohort of 16 adult and one pediatric patients who were identified with two or more PVs/LPVs in cancer predisposition genes.

II. Methods

This study is a retrospective case review of 17 hereditary cancer orders that were identified to have two or more PVs/LPVs in different genes. Patients were tested on one of three hereditary cancer tests: *BRCA1/2*, a Lynch syndrome panel, or a comprehensive multi-gene cancer panel. Analyzed data included test results, variant classification, and reported personal cancer history.

III. Results

Only one patient with double germline variants was reported with a personal history of more than one type of cancer. The patient (#9 in **Table 1**) reported multiple cancers and ages of diagnoses: breast, 59; colorectal, 65; and endometrial, 73. She was identified to have two pathogenic variants: *ATM* c.3372C>G and *MUTYH* c.1187G>A.

In the study:

- Twenty-seven different variants in 13 unique genes were identified with *MUTYH*, *BRCA2*, and *BRCA1* occurring most frequently (**Figure 1**).
- Three unique *MUTYH* variants were found in ten patients.
- Six unique *BRCA2* and five *BRCA1* variants were observed in seven and five patients, respectively.
- Sixteen PVs and 11 LPVs were identified across the cohort. The majority of patients (6, 35%) had a personal history of breast cancer (mean age of diagnosis 41) (**Figure 2**).
- Colorectal cancer (CRC) (17.6%) was the second most common cancer (3, mean age of diagnosis 48).
- Other personal histories of cancer included: ovarian (2, ages 46, 67), and gastric (1, age 34).
- Three patients reported no personal cancer history, one did not provide history, and two reported colon polyps.

Figure 1: Distribution of Hereditary Cancer Genes Across Cohort (n=13)

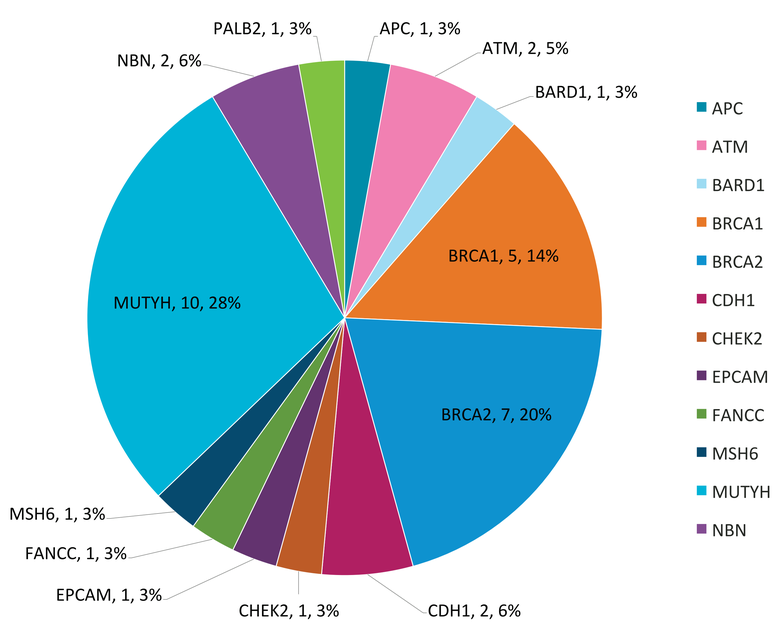

Figure 2: Personal Cancer Histories of Cohort (n=17 patients)

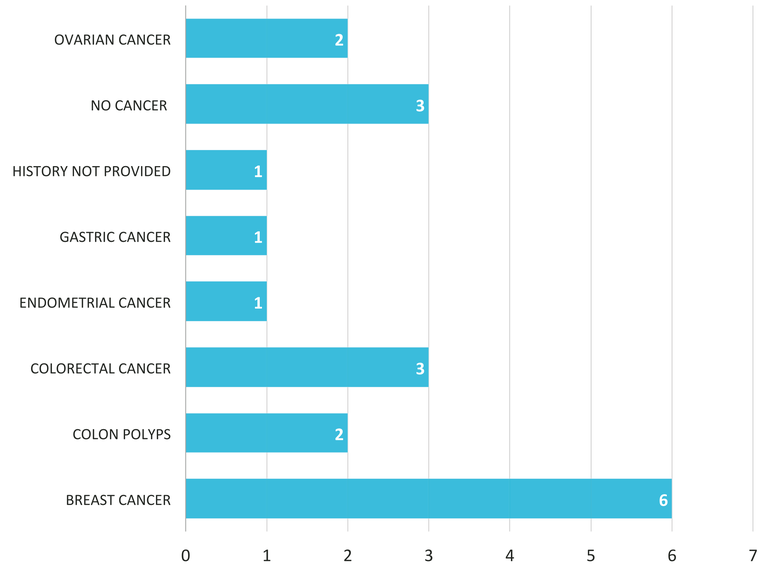

Table 1: Patient Genotype and Phenotype Data

Patient	Genes	Variants	Classifications	Gender	Personal Cancer History	Age at Diagnosis	Age at Testing
1	*BRCA2*	c.5946delT	PV	F	No cancer diagnosis	N/A	51
	CHEK2	c.1283C>T	LPV				
2	*BRCA2*	c.1796_1800delCTTAT	PV	F	Breast	43	51
	BRCA2	c.4092_4093insAA	LPV				
3	*BRCA2*	c.5946delT	PV	F	Breast	45	45
	ATM	c.8293G>A	LPV				
4	*FANCC*	c.1642C>T	PV	F	Colorectal	56	58
	MUTYH	c.1187G>A	PV				
5	*BRCA1*	c.5289delG	PV	F	Breast	33, 52	54
	BARD1	C.1315-2A>G	LPV				
6	*BRCA2*	c.1929delG	PV	F	No cancer diagnosis	N/A	27
	MUTYH	c.1187G>A	PV				
7	*BRCA1*	c.1175_1214del40	PV	F	Ovarian	47	47
	MUTYH	c.1187G>A	PV				
8	*CDH1*	c.1137+1G>A	PV	F	Gastric	34	46
	MUTYH	c.1435G>T	LPV				
9	*ATM*	c.3372C>G	PV	F	Breast Colorectal Endometrial	59 65 73	74
	MUTYH	c.1187G>A	PV				
10	*BRCA1*	EXON 2 DELETION	PV	F	Breast	42	42
	MUTYH	c.933+3A>C	PV				
11	*APC*	c.3927_3931delAAAGA	PV	M	Adenomatous Colon Polyps	9	9
	MUTYH	c.1187G>A	PV				
12	*MUTYH*	c.1187G>A	PV	F	Colon Polyps	Not provided	63
	CDH1	c.2430delT	LPV				
13	*BRCA2*	c.7758G>A	PV	F	Breast	25	28
	NBN	c.481-2A>T	LPV				
14	*BRCA2*	c.4570_4573delTTTC	LPV	F	Ovarian	67	67
	PALB2	c.3297_3298insT	LPV				
15	*EPCAM*	DELETION EXONS 8-9	PV	M	Colorectal	23, 36	37
	MUTYH	c.1187G>A	PV				
16	*MUTYH*	c.1187G>A	PV	F	Not provided	Not provided	37
	NBN	c.1515DELG	LPV				
17	*MSH6*	DELETION OF EXON 1	LPV	F	No cancer diagnosis	N/A	49
	BRCA1	c.4986+6T>C	PV				
	BRCA1	DELETION OF EXONS 1-2	PV				

IV. Discussion

Clinical genetic testing laboratories are well positioned to identify patients harboring variants in multiple cancer predisposition genes. In this study, the average age of an initial cancer diagnosis was about 36 years. On average patients waited six years (range 0-21 years) between cancer diagnosis and undertaking genetic testing (average age of 42 years). This suggests an opportunity for these patients to have begun earlier surveillance for a second primary cancer than is typically recommended for the general population. Patient 9 was 74 years old and already experienced three cancers when she learned of her two PV (*ATM* and *MUTYH*). In contrast, Patient 17 who was identified at age 49 with two PV in *BRCA1* and one LPV in *MSH6* had remained cancer free. The data suggest the need for additional long-term data collection, as the cohort age increases, to evaluate the need and timing of genetic testing, early screening and interventions. With continued collaboration between clinicians and laboratories, phenotypic correlations will better predict cancer risks and improve medical management for this population of patients.

V. Reference

1. Whitworth J et al. Multilocus Inherited Neoplasia Alleles Syndrome. *JAMA Oncology* 2(3):373-379, 2016.

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