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Cancer risks associated with pathogenic variants in the ataxia telangiectasia mutated (*ATM*) gene

Michael J. Hall, MD, MS[1]; Katie Larson, MS[2]; Ryan Bernhisel, MStat[2]; Elisha Hughes, PhD[2]; Eric Rosenthal, PhD, ScM[2]; Nanda Singh, PhD[2]; Johnathan M. Lancaster, MD, PhD[2]; Allison W Kurian, MD, MSc[3]

[1]Fox Chase Cancer Center, Philadelphia, PA; [2]Myriad Genetic Laboratories, Inc., Salt Lake City, UT; [3]Stanford University, Palo Alto, CA

BACKGROUND

- Germline pathogenic variants (PV) in *ATM* are considered low-to-moderate penetrance risk factors for breast cancer, conferring two-fold increased risk.
- Women with *ATM* PV are eligible for breast MRI and follow-up in a high-risk clinic.
- *ATM* PV also have known/suspected associations with increased risks for other cancers, including pancreatic, ovarian, prostate and gastric. Guidelines for cancer prevention beyond breast are generally lacking due to uncertain penetrance estimates.
- Further, it remains uncertain how PV type (truncating versus missense) and PV position impact penetrance, with some studies suggesting the c.7271T>G PV may be high penetrance for breast cancer.
- We investigated cancer risks with *ATM* PV in a large clinical testing dataset.

METHODS

- Individuals (627,742) undergoing commercial testing with a multi-gene hereditary cancer panel (09/2013-07/2019) were reviewed for individuals who tested positive for a single PV in *ATM,* or negative for any PV.
- PV included variants classified as suspected deleterious or deleterious (hereafter pathogenic).
- Patient age, sex, ancestry, personal/family cancer history were extracted from a healthcare provider-completed test requisition form.
- *ATM* PV were analyzed together and by PV type: truncating, missense (excluding c.7271 T>G), and the single high penetrance missense variant c.7271 T>G.
- Risks were estimated using multivariate logistic regression and are reported as odds ratios with 95% confidence intervals (CI).

RESULTS

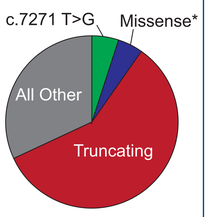
- Single *ATM* PV were identified in 0.7% (4,607/627,742) of individuals within this commercial testing cohort (Table 1).
- The majority of *ATM* PV carriers had a truncating mutation (58.3%; Figure 1).
  - The single missense variant c.7271 T>G was highly prevalent, comprising 5.0% of all *ATM* PV detected.
  - Individuals did not differ demographically based on PV type, except for a slight enrichment in white/non-Hispanic individuals with c.7271 T>G (77.7%) vs. truncating and missense PV (60.2% and 69.5%, respectively).

Table 1. Patient Characteristics for ATM Positive and Negative Patients

Variable	Characteristic	All *ATM* PV (N=4,607)	PV-Negative (N=623,135)
Age at Testing	Median (IQR)	49 (39, 59)	48 (38, 58)
Sex	Female	4,378 (95.0%)	601,246 (96.5%)
	Male	229 (5.0%)	21,889 (3.5%)
Race/ Ethnicity	White/ Non-Hispanic	2,899 (62.9%)	358,097 (57.5%)
	Black/African	289 (6.3%)	51,324 (8.2%)
	Hispanic/Latino	288 (6.3%)	46,713 (7.5%)
	Asian	100 (2.2%)	14,224 (2.3%)
	Ashkenazi Jewish	34 (0.7%)	10,302 (1.7%)
	Native American	31 (0.7%)	5,141 (0.8%)
	Middle Eastern	21 (0.5%)	3,428 (0.6%)
	Other	24 (0.5%)	2,694 (0.4%)
	Multiple	270 (5.9%)	41,021 (6.6%)
	None Specified	651 (14.1%)	90,191 (14.5%)

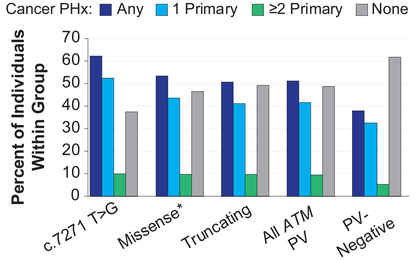
PV-negative: negative for PV in any panel gene and negative for VUS in *ATM*.

Figure 1. ATM PV Type Distribution



*Excluding c.7271 T>G

Figure 2. Personal Cancer History for Individuals with and without ATM PV



p-values for differences between All *ATM* PV and PV-Negative <0.0001; *Excluding c.7271 T>G

- *ATM* PV carriers were more likely to have a personal history of cancer than non-carriers (p<0.0001; Figure 2).
  - Carriers of c.7271 T>G trended towards a greater personal history of a single primary cancer.
- Elevated risks of multiple cancer types were identified in *ATM* PV carriers (Table 2), but not early-onset cancers.
  - *ATM* PV are high penetrance for pancreatic (OR 4.21), gastric (OR 2.97) and prostate cancer (OR 2.58), and low-to-moderate penetrance for invasive ductal breast cancer, DCIS, male breast, melanoma, ovarian and colon cancers.

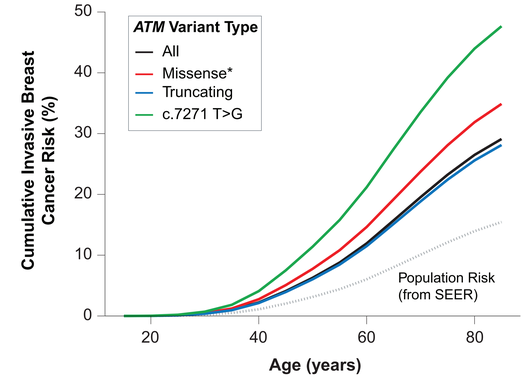
Table 2. Odds Ratios by Cancer and ATM PV Type

ATM PV Type	Cancer	Odds Ratio	95% CI	p-value
All	***Breast Cancer***			
	Invasive	2.03	1.89-2.19	<0.0001
	DCIS	1.80	1.61-2.02	<0.0001
	Lobular	0.94	0.74-1.20	0.6229
	Male	1.72	1.08-2.75	0.0233
	Gastrointestinal Cancers			
	Pancreatic	4.21	3.24-5.47	<0.0001
	Gastric	2.97	1.66-5.31	0.0002
	Colorectal	1.49	1.24-1.79	<0.0001
	Other Cancers			
	Prostate	2.58	1.93-3.44	<0.0001
	Ovarian	1.57	1.35-1.83	<0.0001
	Melanoma	1.46	1.18-1.81	0.0006
	Endometrial	1.10	0.88-1.36	0.4079
Truncating	***Breast Cancer***			
	Invasive	1.95	1.77-2.14	<0.0001
	DCIS	2.05	1.78-2.36	<0.0001
	Lobular	0.90	0.65-1.24	0.5155
	Male	1.51	0.81-2.82	0.1988
Missense*	***Breast Cancer***			
	Invasive	2.52	1.94-3.28	<0.0001
	DCIS	1.47	0.95-2.29	0.0844
	Lobular	1.51	0.74-3.07	0.2561
	Male	1.17	0.15-9.11	0.8804
c.7271 T>G	***Breast Cancer***			
	Invasive	3.76	2.76-5.12	<0.0001
	DCIS	1.70	1.03-2.81	0.0375
	Lobular	0.82	0.26-2.58	0.7344
	Male	8.31	1.46-47.27	0.0170

DCIS, ductal carcinoma *in situ*;*Excludes c.7271 T>G

- Missense PV (OR 2.52) and the c.7271 T>G PV (OR 3.76) are more penetrant for invasive ductal breast cancer than truncating PV (OR 1.95; Table 2).

Figure 3. Cumulative Risk of Invasive Breast Cancer by Age and ATM PV Type Compared to the Overall Population Risk



*Excluding c.7271 T>G

- *ATM* PV carriers have a higher cumulative risk of invasive ductal breast cancer compared to the general population as defined using Surveillance, Epidemiology, and End Results Program (SEER) data, with carriers of the c.7271 T>G variant carrying the highest risk (Figure 3).

CONCLUSIONS

- *ATM* PV are associated with 1.5-fold to >4-fold increased cancer risks across a variety of disease sites, including invasive breast cancer (2-fold increased risk).
- Cancer risks also demonstrate mutation-specific variability, as suggested by the 4-fold increased risk of invasive breast cancer in carriers of the *ATM* PV c.7271T>G.
- Larger and/or pooled studies are critical to further refine the breadth and magnitude of *ATM*-associated cancer risk and to improve clinical management guidelines for *ATM* PV carriers.

CONFLICTS AND ACKNOWLEDGMENTS

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