Observation of Cancers Other Than Breast in Monoallelic *ATM* Gene Mutation Carriers and Their Families

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BACKGROUND

- Ataxia-telangiectasia (AT) patients (biallelic *ATM* mutation carriers) face an increased risk for cancer, particularly hematologic malignancies, whereas monoallelic *ATM* mutation carriers have an increased risk for other cancer types such as breast cancer and pancreatic cancer.[1-4]
- It is estimated that approximately 0.5% of the general population are *ATM* mutation carriers, and with the recent availability of Next-Generation Sequencing (NGS)-based hereditary cancer panel diagnostic testing, an increased number of *ATM* carriers are being identified.
- The Medical College of Wisconsin (MCW) Cancer Genetic Counseling program offers hereditary cancer gene panel testing to patients. Among those receiving panel testing, family histories of pancreatic cancer, melanoma and/or brain cancer were frequently observed for patients with monoallelic *ATM* mutations.

METHODS

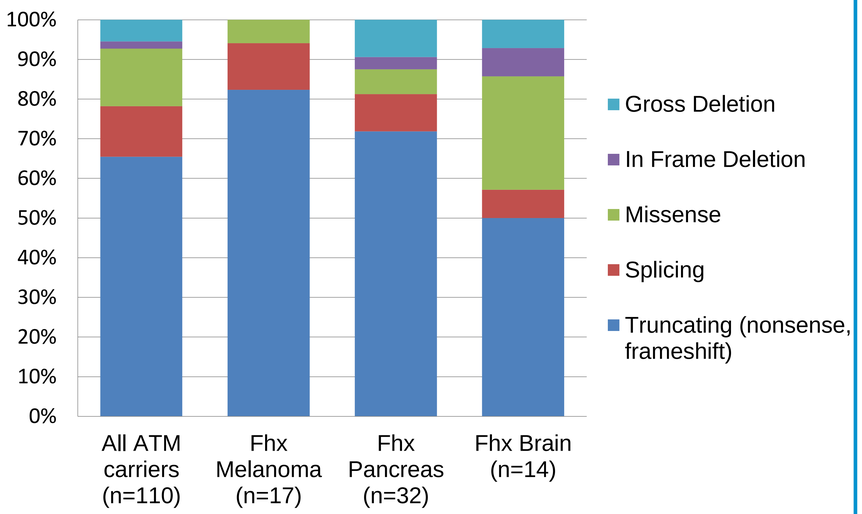
- To test the hypothesis that pancreatic cancer, brain cancer, and melanoma are associated with *ATM* mutations, we compared the prevalence of these cancers among first and second degree relatives of 110 individuals identified to carry an *ATM* pathogenic mutation or likely pathogenic variant and 9021 noncarriers in a clinician-referred cohort of patients undergoing NGS and deletion/duplication analysis of *ATM* as part of multigene panel testing at a clinical diagnostic laboratory (Ambry Genetics, Aliso Viejo, CA).
- Pathogenic mutations and likely pathogenic variants included truncating mutations, as well as missense mutations with strong evidence to support pathogenicity (for example, linked to AT or breast cancer and/or shown to be deleterious by functional studies). Individuals known to carry a mutation in other cancer susceptibility genes were excluded from analysis.

TABLE 1. DEMOGRAPHICS

	ATM-positive cases, n	%	*ATM*-negative controls, n	%
Ethnicity				
African American/Black	2	1.82%	376	4.17%
Alaskan Native	0	0.00%	2	0.02%
Ashkenazi Jewish	6	5.45%	587	6.51%
Asian	2	1.82%	220	2.44%
Caucasian	77	70.00%	6518	72.25%
Hispanic	6	5.45%	329	3.65%
Middle Eastern	0	0.00%	46	0.51%
Mixed Ethnicity	2	1.82%	265	2.94%
Native American	0	0.00%	9	0.10%
Other	0	0.00%	26	0.29%
Unknown	15	13.64%	643	7.13%
Multigene Panel Ordered[1]				
BreastNext	53	48.18%	4505	49.94%
CancerNext	36	32.73%	2328	25.81%
OvaNext	15	13.64%	1932	21.42%
PancNext	6	5.45%	256	2.84%
Total, N	110		9021	

[1] Panels included 14-28 genes

FIGURE 1. *ATM* MUTATION DISTRIBUTION



A variety of mutation types throughout the *ATM* gene were detected in this cohort. Based on the small size of the subgroups of patients with a family history of the selected cancers and limited segregation data, it is likely premature to assess for potential genotype-phenotype associations in this cohort.

Fhx: family history, limited to first- and second-degree relatives

FIGURE 2. SELECTED *ATM* PEDIGREES FROM MCW

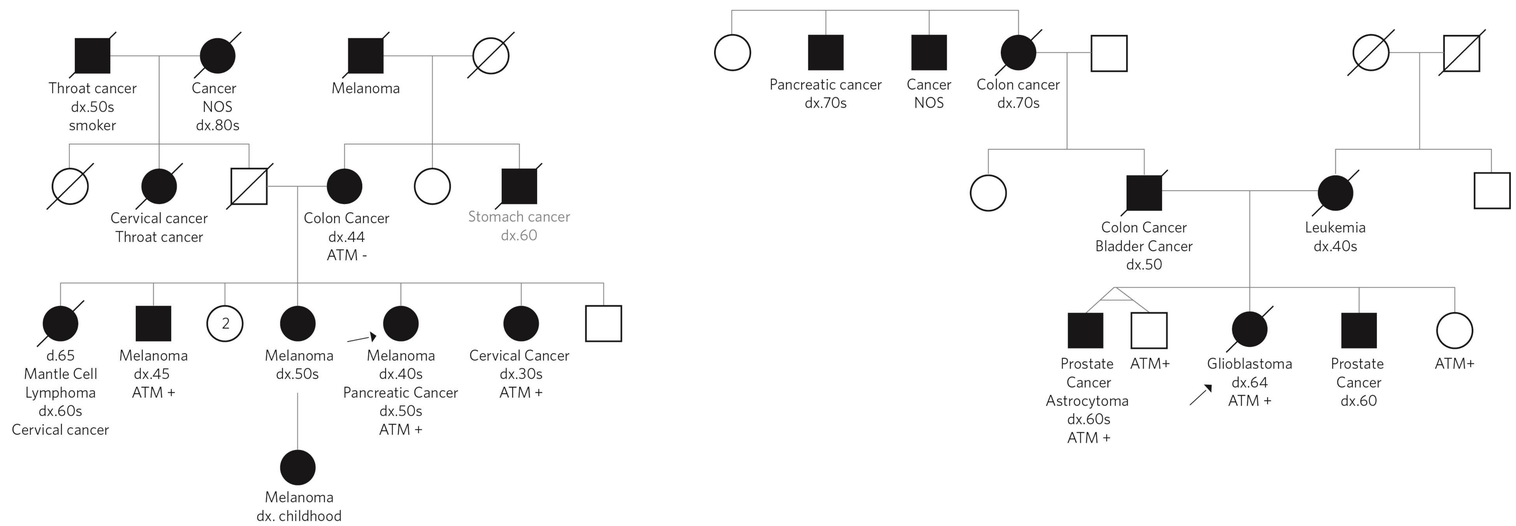


FIGURE 3. FAMILY HISTORY OF SELECTED CANCERS

Fhx: family history, limited to first- and second-degree relatives ★ statistically significant

- *ATM* mutation carriers were 2.3 times more likely to have a family history of pancreatic cancer compared to noncarriers (p-value= 4.7×10^{-5}; 95%C.I.= [1.527, 3.504]).
- *ATM* mutation carriers were also more likely to have a family history of melanoma and brain cancer (melanoma: OR= 1.59; p-value= 0.0785; 95%C.I.= [0.944, 2.679]; brain cancer: OR= 1.69; p-value= 0.0656; 95%C.I.= [0.961, 2.979]). The differences did not quite reach significance, possibly due to the limited number of *ATM* carriers studied.
- In the laboratory-selected cohort of *ATM* mutation carriers, limited co-segregation data was available for probands with a reported family history of melanoma, brain, and/or pancreatic cancers; however, the *ATM* mutation segregated with both glioblastoma and pancreatic cancer in one kindred and likely segregated with one pancreatic cancer in another (patient's father died from pancreatic cancer and her unaffected mother tested negative).

TAKE-HOME POINTS

- In this study, *ATM* mutation carriers were more likely to have a family history of melanoma, brain, and pancreatic cancer than noncarriers; however, only the pancreatic cancer association reached statistical significance. This is consistent with previous literature supporting an association of pancreatic cancer with *ATM* mutation carrier status.
- Future studies such as co-segregation, tumor loss of heterozygosity, and case-control analyses in larger prospective cohorts are needed to confirm these observations and further define the full cancer spectrum associated with *ATM* heterozygosity. This, in turn, will help guide medical management for *ATM* mutation carriers.

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