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

Proposal Number:

997

First Author:

Holly LaDuca, MS
Ambry Genetics
Aliso Viejo, CA

Co-Author(s):

Jennifer Geurts, MS
Medical College of Wisconsin
Milwaukee, WI

Morgan Depas, MS
Medical College of Wisconsin
Milwaukee, WI

Rachel McFarland, BS
Ambry Genetics
Aliso Viejo, CA

Shuwei Li
Ambry Genetics
Aliso Viejo, CA

Emily Hallberg, MPH
Mayo Clinic
Rochester, MN

Fergus J. Couch, Ph.D.
Mayo Clinic
Rochester, MN

Elizabeth Chao, MD
Ambry Genetics
Aliso Viejo, CA

Description:

INTRODUCTION: Mutations in *ATM* are known to cause the autosomal recessive neurodegenerative disorder ataxia-telangiectasia (AT). AT patients face an increased risk for cancer, particularly hematologic malignancies, whereas monoallelic (heterozygous) *ATM* mutation carriers have an increased risk for other cancer types. Breast cancer is the best characterized of the cancers associated with *ATM* carriers, with studies reporting up to a 60% risk for the disease by age 80. *ATM* mutations have also been observed in a number of pancreatic cancer families, yet no cumulative lifetime risk estimates have been published. It is estimated that approximately 0.5-1% 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 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 non-carriers 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. 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.
RESULTS: The prevalence of a family history of pancreatic cancer, brain cancer, or melanoma among *ATM* mutation carriers was 29.1% (n=32), 12.7% (n=14), and 15.5% (n=17), respectively. *ATM* mutation carriers were 2.3 times more likely to have a family history of pancreatic cancer compared to non-carriers (p-value= $4.7x10^{-5}$; 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]), although the differences were non-significant, possibly due to limited numbers of *ATM* carriers studied.
CONCLUSION: Future studies such as co-segregation, tumor loss of heterozygosity analysis, and case-control analyses in 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.

Learning Objectives:

Review current knowledge of cancer risks in ATM monoallelic mutation carriers

Describe clinical histories of ATM monoallelic mutation carriers and their families, as observed in a cancer genetic counseling program

Compare the prevalence of clinically-observed cancers among first and second degree relatives of ATM mutation carriers and non-carriers in a clinician-referred cohort of patients undergoing ATM analysis as part of multigene panel testing at a clinical diagnostic laboratory

Recommend follow-up studies to confirm observations and to aid in guiding medical management for ATM mutation carriers

Keywords:

Cancer Syndromes

Clinical History
Genetic Testing
NextGen Sequencing
Risk Assessment
Sequencing

Primary Topic Focus:

Cancer Genetics

Secondary Topic Focus:

Molecular Genetics/Exome

Each year an ACMG Foundation for Genetic and Genomic Medicine/ Signature Genomics, a PerkinElmer Company Travel Award is given to a selected student, trainee, or junior faculty ACMG member whose abstract submission is chosen as a platform presentation during the 2015 ACMG Annual Clinical Genetics Meeting. In recognition of their selected presentation, Signature Genomics, a PerkinElmer Company covers the travel costs for the recipient to the meeting. Would you like to be considered for the ACMG Foundation/Signature Genomics, a PerkinElmer Company Travel Award?

No

Would you like to be considered for the ACMG Foundation/Carolyn Mills Lovell Award for a Genetic Counselor?

Yes

Please tell us what company or institution awarded a grant for your research? Please list all if more than one.

Multiple authors (Holly LaDuca, Rachel McFarland, Shuwei Li, and Elizabeth Chao) are employed and receive a salary from Ambry Genetics, and multigene panel testing is among the commercially available tests.