Cancer phenotypes of germline monoallelic *ATM* mutation carriers and their families

H. LaDuca, A. Stuenkel, S. Keiles, T. Pesaran, S. Tandy, E. Chen, V. Speare, C. Radford, C. Gau. Ambry Genetics, Aliso Viejo, CA.

Abstract:

Monoallelic ATM mutations have been associated with an increased risk of both breast and pancreatic cancers. ATM sequence and gross deletion/ duplication analyses are included in three hereditary cancer panels offered by our laboratory, and to date, 26 ATM pathogenic mutation carriers have been identified. The purpose of this study is to describe the clinical characteristics of these ATM mutation carriers and their families. Retrospective test requisition form review was used to obtain clinician-reported clinical history information, including patient clinical history, testing history, and family history, for all pathogenic ATM mutation carriers. Follow-up contact with referring providers yielded additional clinical data for select patients. Chi-square analysis was used for statistical comparison of the observed mutation frequency in our Caucasian patients with that expected in the European American general population. All 26 ATM mutation carriers had a reported personal history of cancer, with 9 (34.6%) having a personal history of more than one primary cancer diagnosis. All but one patient (n=25) also had a family history of cancer. The spectrum of primary cancers observed in our ATM probands included breast, pancreatic, colorectal, ovarian, fallopian tube, leukemia, lymphoma, lung, basal cell carcinoma, cervical, and squamous cell carcinoma of the perineum. Twenty (76.9%) ATM carriers had a personal history of breast cancer, with an average age of 43 at first breast cancer diagnosis (range 31-69 years). Four (20.0%) of these breast cancer patients had a history of more than one primary breast cancer. Seven (26.9%) carriers had personal and/or family history of pancreatic cancer. BRCA1/2 testing information was reported for 18 (69.2%) mutation carriers, and all reported results were negative. The observed frequency (1.8%) of pathogenic ATM mutations in our Caucasian patients was significantly elevated compared to the frequency in the European American general population (0.4%) (OR=4.84, $p=1.3\times10-7$, 95% CI= 2.54-9.25). Despite the selection bias of our testing population and the limitations of clinician-reported clinical history details, our data contributes to the growing body of literature on cancer risks in monoallelic ATM mutation carriers. Efforts are being made to determine co-segregation of mutations with disease in these families and will increase our knowledge of the penetrance of mutations in families and any additional cancer associations.