Missense ATM Variant c.6919C>T (p.Leu2307Phe) May Be Associated with Breast Cancer Risk But Not Ataxia Telangiectasia

**BACKGROUND**
- Individuals with rare autosomal dominant variants (PMVs) in ATM are at increased risk of breast cancer and pancreatic cancer, as well as possibly increased risk to aggressive prostate cancer and other malignancies.
- Individuals with inherited ATM and Ataxia Telangiectasia (AT) typically maintain fertility and severe clinical disease is uncommon.

**METHODS**
- Exome data from breast cancer cases and controls were analyzed for both rare and inherited variants in ATM.
- The variant was associated with a previously described loss-of-function signature of ATM carriers.
- Variants were then analyzed in relative cases with breast cancer.
- The variant was found to cause a loss-of-function effect in ATM.

**CONCLUSIONS**
- Centromeric c.6919C>T ATM variants are associated with increased breast cancer risk, but not reoccurrence ATM the breast.
- The variant is the first ATM variant that is a heterozygous homologous with proven risk of breast cancer.
- The results suggest that ATM mutations may have implications for how ATM variants are classified, as well as for exceptions influencing the classification of other hereditary cancer genes with recessive phenotypes.


Myriad Genetic Laboratories, Inc.

**PRESENTED AT:**
BRCA 2021
A Vision of the Future
Une vision pour l'avenir

BACKGROUND

- Individuals with monoallelic pathogenic variants (PVs) in \( ATM \) have increased risks for female breast and pancreatic cancer, as well as possibly increased risks for aggressive prostate cancer and other malignancies.

- Individuals with biallelic PVs in \( ATM \) have Ataxia Telangiectasia (AT), typically manifesting diverse and severe clinical features in childhood.

- Although variants in \( ATM \) are presumed to be pathogenic for both phenotypes, we find that monoallelic carriers of the variant c.6919C>T (p.Leu2307Phe) (Figure 1) may have an increased risk for cancer, although biallelic carriers do not have clinically-apparent AT.

- It has been reported that this variant is associated with an increased breast cancer risk in heterozygous individuals.\(^1\)
METHODS

- De-identified clinical information from provider-completed test request forms was evaluated for both monoallelic and biallelic carriers of \( ATM \) c.6919C>T.

- The variant was assessed with a previously-described history weighting algorithm (HWA) comparing variant-associated cancer histories to histories of matched controls with known PVs in the same gene and matched controls with no PVs.2

- A multivariate logistic regression model was used to estimate odds ratios (ORs) for breast cancer, reported with 95% confidence intervals (CIs). The model produced ORs that were adjusted for age at testing, ethnicity, and personal and family cancer history.
FIGURES

Figure 1. ATM Gene Map and c.6919C>T location

Figure 2. HWA for ATM c.6919C>T. Curves represent pathogenic and benign controls. HWA has been validated with >99.5% positive and negative predictive values.

Figure 3. Odd Ratios (with 95% CI) for Female Breast Cancer
RESULTS

- The HWA indicates $ATM\ c.6919C>T$ is associated with increased cancer risk with a high degree of confidence, based on 1,760 observations (Figure 2).

- The allele frequency is 3.08% in the Ashkenazi Jewish population per gnomAD, and we have identified over 3,200 monoallelic carriers of primarily Ashkenazi Jewish ancestry.

- No clinical features of AT have been reported for any of the 40 homozygous carriers observed by our laboratory (median age 55 years).

- The OR for female breast cancer in monoallelic women was calculated as 1.59 (95% CI 1.33-1.76), compared to 2.03 (95% CI 1.89-2.19) for previously-established $ATM$ PVs (Figure 3).
CONCLUSIONS

- Monoallelic c.6919C>T ATM variants are associated with increased cancer risk, but not recessive AT in the biallelic state.

- To our knowledge, this is the first ATM variant that in a heterozygous state is associated with cancer, but does not cause AT when homozygous. This has implications for how ATM variants are classified, as well as for assumptions influencing the classification of other hereditary cancer genes with recessive phenotypes.
DISCLOSURES

All of the authors worked for Myriad Genetic Laboratories, Inc. at the time of the study. They received salaries and may have received stock/stock options as part of their compensation.
REFERENCES

