EXAMINING SEVERITY OF CANCER HISTORY IN PATIENTS WITH PATHOGENIC VARIANTS IN *ATM*

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BACKGROUND

- Germline pathogenic variants (PVs) in the *ATM* gene are known to cause the recessive condition Ataxia-Telangiectasia (A-T), a neurodegenerative disease.[1]
- Individuals with a single *ATM* PV are known to have an increased risk for female breast cancer and pancreatic cancer.[2,3]
- Published reports differ on the theory of a particular type of PV in *ATM* conferring a different level of cancer risk.[4-6] We tested the hypothesis that different types of PVs confer different levels of cancer risk by comparing the cancer histories of individuals carrying different types of PVs.

METHODS

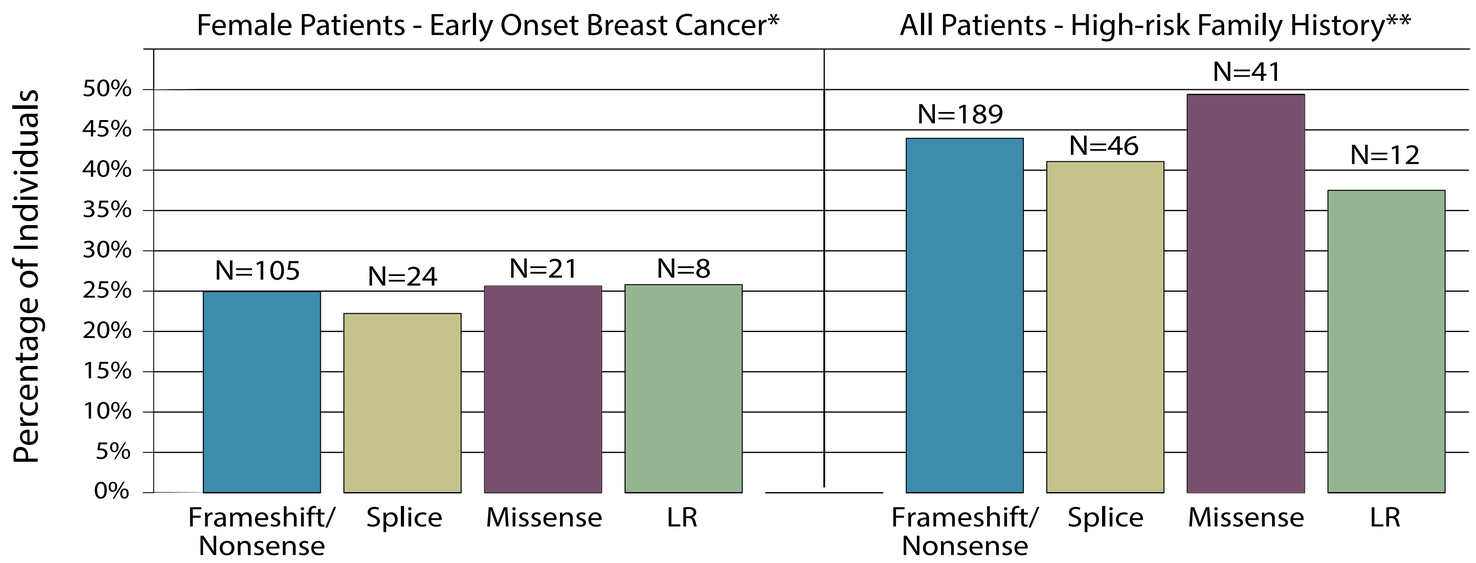
- Individuals ascertained for suspected hereditary cancer risk were tested with a clinical 25-gene hereditary cancer panel between September 20, 2013 and June 12, 2015.
- Clinical information for those with PVs in *ATM* was obtained via healthcare provider report on the test request forms.
- Variants with a laboratory classification of Deleterious or Suspected Deleterious were regarded as pathogenic.
- 33 individuals with PVs in *ATM* and another gene were excluded from the cohort.
- Missense variants in *ATM* were classified as pathogenic if they are known to contribute to the classic form of A-T. The missense PV c.7271T>G (p.Val2424Gly) may carry higher cancer risks than other PVs in *ATM*.[7,8] For this reason, we examined this variant separately from other missense PVs.

RESULTS

Table 1. Pathogenic Variant Types in *ATM*

Mutation Type	Male	Female
Frameshift/Nonsense	9	421
Splice	4	108
Missense	1	82
Large Rearrangement	1	31
Total:	15	642
Total Mutations:	657	

Figure 1. Pathogenic Variant Types in *ATM* According to Personal and Family History



*Diagnosed at or before age 50. **3 or more diagnoses of breast and/or pancreatic cancer in the family, including the patient where applicable.

- In total, 657 individuals were found to carry a PV in *ATM* (Table 1).
- Approximately 25% of women with different types of PVs in *ATM* had a personal diagnosis of breast cancer at or before age 50 (Figure 1).
- 33 individuals (32 women, 1 man) were found to carry the variant c.7271T>G.
- 11/32 (34.4%) women with c.7271T>G had a personal diagnosis of early onset breast cancer.
- 10/50 (20.0%) women with a different missense PV had a personal diagnosis of early onset breast cancer.
- Between 35% and 50% of all individuals with different types of PVs had a high-risk family history (Figure 1).
  - High-risk family history was defined as 3 or more diagnoses of breast and/or pancreatic cancer in the family, including the patient where applicable.

CONCLUSIONS

- This study identified no significant difference in cancer risks associated globally with different types of PVs.
- It appears that there is no evidence that variants in *ATM* present unique challenges for classification, although we cannot rule out higher or lower penetrance associated with individual variants.
- Women with the missense PV c.7271T>G were more likely to have a personal diagnosis of breast cancer ≤ 50 compared to women with other missense PVs, although this difference was not statistically significant.
- As additional families are identified, these findings can be confirmed and the relative cancer risks associated with individual *ATM* variants can be further characterized.

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Presented at ASHG - October 8, 2015