Authors:
R. Pilarski[1], S. Li[2], R. McFarland[2], H. LaDuca[2], B. Smith[2], T. Pesaran[2]

Institutions:
1) Division of Human Genetics, Comprehensive Cancer Center, Ohio State Univ, Columbus, OH.; 2) Ambry Genetics Corp, Aliso Viejo, CA

Title:
The *PTEN* promoter: to be or not to be included on multigene panel tests?

Abstract:

Background

Pathogenic *PTEN* alterations have been associated with an increased risk of developing cancers of the breast, thyroid, endometrium, and others as part of *PTEN* hamartoma tumor syndrome. Although several alterations in the *PTEN* promoter region have been described as mutations, data are insufficient to support a classification of pathogenicity and they are currently characterized as variants of unknown significance (VUS) by clinical labs. We sought to assess the association of *PTEN* promoter variants with breast and other cancers in a cohort of 61,552 patients undergoing *PTEN* testing.

Methods

Clinical histories of patients who underwent comprehensive *PTEN* analysis from January 1, 2014 to March 31, 2016 as part of a multigene panel testing (MGPT) were retrospectively reviewed. Personal and family cancer histories of *PTEN* promoter variant carriers (PV; N=704) were compared against *PTEN* mutation-positive patients (MP; N=57) and also matched mutation-negative individuals (WT; N= 2,194). The frequency of MP, PV and WT were compared between patients with and without selected cancer phenotypes using the Fisher's exact test and multivariate logistic regression analysis, controlling for age at testing, MGPT ordered, ethnicity and gender. Age differences were tested using Welch t-test or Wilcoxon rank test based on the data distribution.

Results

PTEN promoter variants were observed with a frequency of 1.1% (704/61,552). PV individuals were significantly less likely than MP individuals to have a personal history of female breast cancer (p=0.003), bilateral breast cancer (p=0.014), uterine cancer (p=0.001), or kidney cancer (p=0.002). No differences were observed when comparing personal history of colon cancer or thyroid cancer, or family history of female breast cancer among first degree relatives between these two groups. No significant differences were observed when comparing PV individuals with to WT individuals. MP individuals had a younger diagnosis age of female breast cancer (p=0.022; p=0.021), endometrial cancer (p=0.027; p=0.015) and thyroid cancers (p=0.042; p=0.032) compared to WT and PV individuals, respectively.

Conclusions

In this cohort, *PTEN* promoter variants were not associated with an increased risk of *PTEN*-related cancers. These results do not support the inclusion *PTEN* promotor sequencing on cancer panels, as the identification of these alterations contributes to increased VUS burden without increasing diagnostic yield.

Publication Status:
The work outlined in this abstract Has not been published elsewhere.
The work outlined in this abstract Has not been accepted for future publication.

Relationship(s) to Disclose: No